THIRD ANNUAL REPORT OF THE DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES

Research for Better Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service • National Institutes of Health

Front cover
Study of the DNA molecule enables researchers to understand the process by which genetic information is translated into formation of normal or abnormal cellular constituents. Such understanding can lead to better treatment of genetic diseases such as cystic fibrosis and sickle cell anemia.

Third Annual Report of the Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

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Preface

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is responsible for a national program of research on a wide spectrum of diseases affecting virtually every family in the Nation. These diseases are among the most common, chronic, disabling and costly facing this country; they affect over 40 percent of our population, exact an enormous toll in terms of human suffering, and their economic impact exceeds $100 billion annually.

These diseases, despite their apparent disparity, share fundamental mechanisms that results in a unique symbiotic and synergistic effect on the Institute's research programs. New knowledge generated in one group of diseases clarifies and contributes to progress in the fight against the others. Thus, the Institute represents a unique entity: externally it serves multiple interests, but internally its programs are intertwined and benefit from this close relationship.

The Health Programs Extension Act of 1980 requires that the Director of NIADDK provide the President and the Congress an annual report on the Institute's progress in its research attack on these diseases. This *Third Annual Report of the Director, NIADDK* provides a chronicle of the numerous and impressive research advances of the year just finished, the opportunities they present for further research, and the plans developed to meet future needs.

The research achievements described here reflect an explosion of new and promising knowledge that we are witnessing today. This would not be possible without the original ideas and dedicated efforts of the talented research workers who spearhead our fight against chronic and disabling diseases, and the credit for these advances should thus go to them.

I hope that this third annual report will be as informative and gratifying to its readers as were its two predecessors.

Lester B. Salans, M.D.
Director
National Institute of Arthritis,
Diabetes, and Digestive and Kidney Diseases

Executive Summary

Section 434(e) of the Public Health Service Act (as amended by the Health Programs Extension Act of 1980, Public Law 96-538) requires an annual report to the President and to the Congress from the Director of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases on the Institute's progress toward its broad and varied goals in the disease areas under its purview.

In response to this directive, the Third Annual Report of the Director, NIADDK, highlights the Institute's ongoing programs, recent achievements, and plans for future activities in arthritis, diabetes, digestive diseases, kidney diseases, and the many related and other diseases for which it bears responsibility. The report is organized by research focus, with chapters II through V presenting the research accomplishments, special programs, and program plans of each of the four major areas of responsibility of the Institute. These chapters are preceded by an overview of the Institute's structure and activities (chapter I) and followed by the annual reports on the evaluation of the Institute's multipurpose centers programs (chapter VI).

The first chapter describes briefly the Institute's place within the National Institutes of Health and its role in the health research community. The NIADDK's organization and mission are described in detail, with emphasis on the many diseases within the Institute's purview. Also reviewed and contrasted are the various mechanisms of support used by the NIADDK to foster laboratory and clinical research and research training. Summarized here are the Institute's activities in fundamental and clinical biomedical research, research manpower development, disease prevention, technology assessment and transfer, program planning and analysis, and evaluation. There is a section on financial resources, in historical perspective, which portrays graphically the overwhelming emphasis placed by the Institute on investigator-initiated research grants evaluated by the scientific peers of the applicant. Approximately 85 percent of the extramural obligations of the NIADDK are devoted to this mechanism. Finally, there is a section on awards and honors bestowed during the past year on grantees, Institute consultants, and Institute staff.

Reflected in this initial chapter, as well as in later ones, is the sense of excitement generated by recent breakthroughs in science in their application to the endocrine, metabolic, nutritional, digestive, renal, blood, skin, bone, and joint diseases for which the Institute is responsible. Such techniques as cloning and transcription of genetic material, molecular analysis and controlled biosynthesis, applications of monoclonal antibodies, and especially the new interdisciplinary convergences seen in immunologic, genetic, and molecular biologic studies of mechanisms of cell function and of disease, have led to major new developments in work under NIADDK support. These advances are revolutionizing our understanding of and our clinical approaches to the diseases discussed in this volume.

Examples of this progress include the treatment of the nephritis of systemic lupus erythematosus with monoclonal antibodies to DNA; the discovery of potential markers, on the gene level, to identify susceptibility to each of the two types of diabetes; the clinical trial of man-made human growth hormone produced by bacteria and the synthesis of the brain hormone regulating growth hormone release; further definition of the immunologic defects underlying the inflammatory bowel diseases and primary biliary cirrhosis; the use of the hormonal form of vitamin D in the treatment of postmenopausal osteoporosis; extensive experience with a new drug, cyclosporine, for immunosuppression in both kidney and liver transplantation; and the gene-level redirection of hemoglobin synthesis to correct the clinical signs of anemia.

The next four chapters are devoted to specific research advances and Institute plans under four broad subject groupings: II. Arthritis, Musculoskeletal, and Skin Diseases; III. Diabetes, Endocrinology, and Metabolic Diseases; IV. Digestive Diseases and Nutrition; and V. Kidney, Urologic, and Hematologic Diseases. In each of these chapters, there is first an overview of the scope of Institute concerns (corresponding to the branch-level programs of each Division, in general), followed by highlights of research advances. Altogether, significant advances are reported in research and development related to more than 70 diseases and medical therapies with a major impact on the national health scene. In addition, these four chapters outline the NIADDK's plans for continued contributions to im-

provements in biomedical knowledge, treatment and prevention methods, and research skills that, collectively, will make a crucial difference in the outlook for eventual prevention or cure of many chronic and disabling diseases.

The volume concludes with the annual evaluation reports of two important NIADDK programs: the Multipurpose Arthritis Centers and the Diabetes Research and Training Centers. In past years, these reports—which are also congressionally mandated—were transmitted to the Congress as separate documents. They are incorporated in this overall annual report to afford the reader an improved, all-inclusive overview of the Institute's progress. Each of the two reports in chapter VI provides examples of research and programmatic accomplishments of the centers supported under the two programs. Particular attention is devoted to the educational and community health services projects sponsored by the centers. Center evaluation is discussed, and evidence is provided for the thesis that the sharing of resources, which is fundamental to the concept of these programs, both within centers and among centers, results in significantly enhanced productivity.

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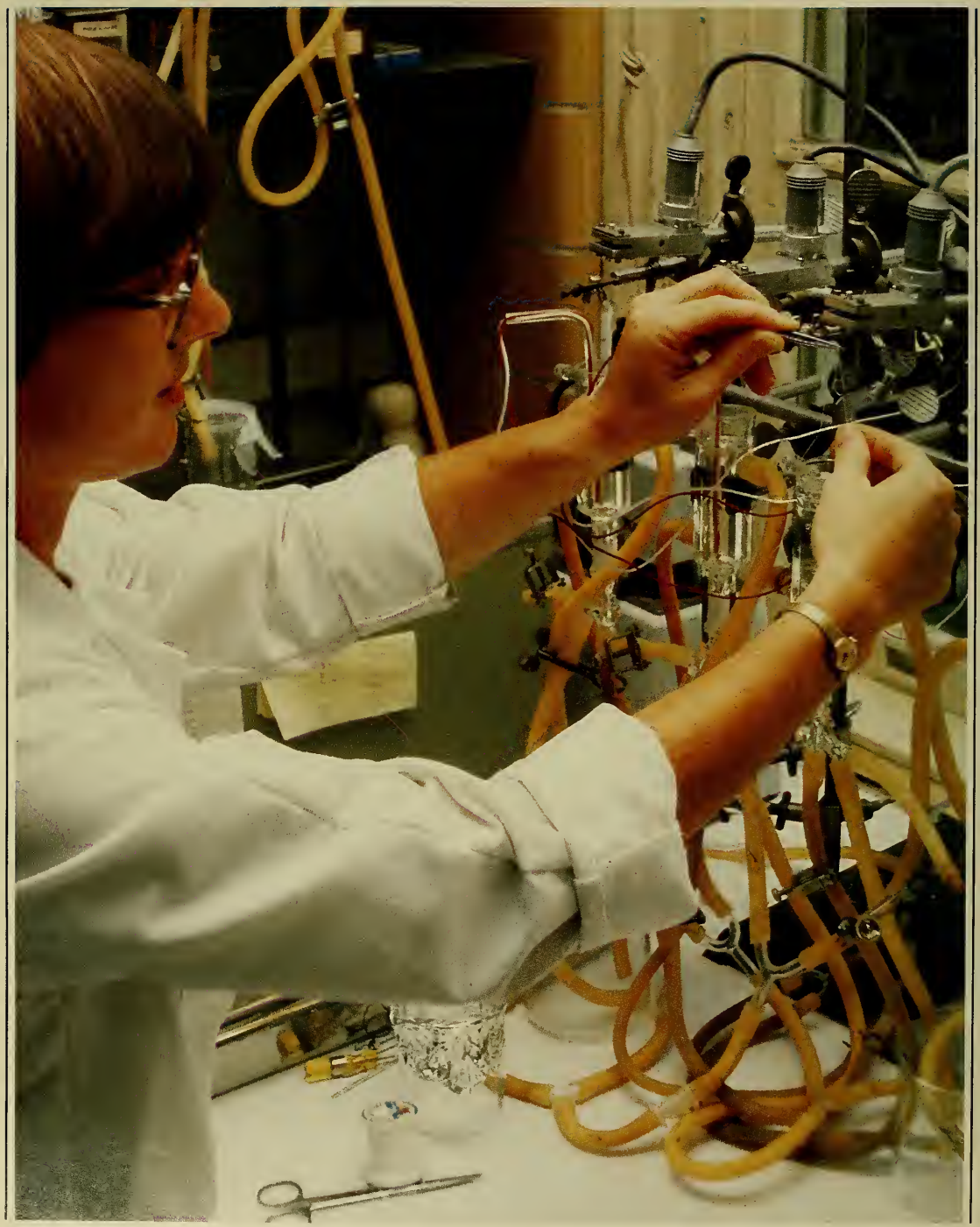


I. NIADDK Mission and Strategies

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is 1 of 11 Institutes known collectively as the National Institutes of Health (NIH), the largest biomedical research organization in the world. The NIH incorporates hundreds of sophisticated research laboratories, clinical care facilities, administrative offices, and a national medical library—all dedicated to fulfilling the agency's role as the spearhead of the Nation's biomedical research effort. To accommodate varying research needs and facilitate progress, each of the 11 NIH Institutes functions as a separate administrative unit within which research activities in one or more disease areas or health problems are planned, coordinated, carried out, and supported.

The NIADDK's efforts to uncover the causes of chronic and disabling diseases have earned its recognition as an Institute whose responsibilities are attuned to the pressing health problems of the American public and whose accomplishments often profoundly affect the disease interests of other Institutes as well.

The focus on basic research that has guided the NIADDK's programs is grounded in the fact that a basic understanding of the intrinsic nature of each disease is imperative for the formation of appropriate, effective strategies for prevention and therapy. Thus, the Institute has an important stake in the pursuit of research using the fundamental sciences, such as biochemistry, biology, physics, chemistry, pathology, genetics, immunology, physiology, and pharmacology, which provide the foundation of knowledge about diseases that can affect many organs or organ systems.

The basic research successes achieved through the NIADDK's programs have been impressive, and those laboratory successes are meaningfully applied to improvement of the Nation's health through clinical studies and trials and programs of technology transfer, information dissemination, and coordination with professional and voluntary groups as well as other government agencies.

NIADDK'S Mission and History

The Institute was established in 1950 through the Omnibus Medical Research Act and started its activities as the National Institute of Arthritis and Metabolic Diseases. Its subsequent history and activities are described extensively in the First Annual Report of the Director of NIADDK (NIH Publication No. 82-2375, September 1982). The mission of the Institute and its scope of research have broadened significantly with the passage of time. In 1982, the Institute was designated a Bureau of the NIH, joining the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Library of Medicine at that level. Exhibit 1 describes representative examples of the NIADDK's present areas of research responsibility.

The National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council provides advice on NIADDK programs and funding of awards.

Facing page
Basic research is conducted and supported by the NIADDK to achieve its goal of developing knowledge concerning the diseases under its purview and thus to achieve the prompt diagnosis, effective treatment, and prevention of these diseases.

EXHIBIT 1. NIADDK research areas: some representative examples

DIVISION OF ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES

Arthritis and Related Disorders

Rheumatoid arthritis
Osteoarthritis
Juvenile arthritis
Systemic lupus erythematosus
Gout
Lyme arthritis
Epidemic polyarthritis
Psoriatic arthritis
Inherited connective tissue diseases
Systemic sclerosis (scleroderma)
Spondyloarthropathies
Muscle structure and function
Muscle pathophysiology

Musculoskeletal Diseases

Scoliosis
Osteoporosis
Osteogenesis imperfecta
Bone transplantation
Bone metabolism
Bone fractures and healing
Artificial joints and biomaterials
Congenital and acquired skeletal anomalies
Low back pain
Exercise pathophysiology
Osteoarthritis

Skin Diseases

Psoriasis
Acne
Mechanisms of retinoid action on skin
Bullous diseases
Ichthyosis
Vitiligo
Eczematous and immunologic diseases
Allergic dermatoses
Cutis laxa
Photobiology
Heritable skin disorders

DIVISION OF DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES

Diabetes

Insulin-dependent diabetes
Noninsulin-dependent diabetes
Complications of diabetes
Etiologic factors in diabetes
Immunology and diabetes
Insulin receptors
Insulin resistance
Insulin delivery devices
Pancreatic islet cell transplantation
Nutrition and diabetes
Animal models of diabetes

Endocrine Diseases

Disorders of endocrine glands (thyroid, pituitary, etc.)
Hormone synthesis, secretion, action, and interactions
Hormonal imbalances
Research availability of hormones
Growth factors
Recombinant DNA production of peptide hormones
Neuroendocrinology and brain peptides
Hormones and pharmacotherapy

Metabolic Diseases

Inborn errors of metabolism
Animal models of inborn metabolic errors
Cystic fibrosis
Enzyme structure and function
Cellular oxidation and biological membranes
Cell surface receptors
Reye's syndrome
Noninvasive instrumentation in metabolic research

DIVISION OF DIGESTIVE DISEASES AND NUTRITION

Esophageal, Gastric, and Colonic Diseases

Ulcer disease
Functional bowel disorders
Gastrointestinal motility dysfunctions
Inflammatory bowel diseases
Gastrointestinal bleeding
Endoscopy in research, diagnosis, and treatment
Gastrointestinal growth and regeneration
Structure, function, and disease of the esophagus and stomach
Anal-rectal diseases and disorders

Intestinal and Pancreatic Diseases

Gastrointestinal hormones
Small intestine structure and function
Intestinal digestion, absorption, and secretion
Malabsorption syndromes
Diarrheal diseases, celiac sprue
Structure and function of the exocrine pancreas
Pancreatitis
Small intestine and pancreas transplantation
Salivary gland structure, function, metabolism, and diseases

Liver and Biliary Tract Diseases

Hepatitis
Cirrhosis
Genetic liver disease
Hepatic transport defects
Cholesterol and pigment gallstones
Cholesterol and bile acid metabolism
Liver regeneration
Liver transplantation
Portal hypertension and varices
Liver coma

Nutrition

Nutritional requirements in health and disease
Obesity
Regulation of fuel mobilization and storage
Exercise and energy metabolism
Nutritional needs in disease
Nutritional status assessment
Dietary fiber
Essential trace elements and minerals
Nutrient transport, utilization, and function
Special supportive nutrition in disease

DIVISION OF KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

Renal Physiology and Pathophysiology

Renal metabolism and transport
Renin and hemodynamics
Hypothalamic regulation of water balance
Immunologic basis of renal disease
Glomerulonephritis
Interstitial nephritis
Acute renal failure

Urologic Diseases

Nephrolithiasis and urolithiasis
Congenital anomalies of the urinary tract
Bladder dysfunction
Vesicoureteral reflux
Urinary tract infection
Prostatic hypertrophy
Prostatitis

Chronic Renal Diseases

End-stage renal disease
Dialysis therapy
Renal dialysis and its complications
Kidney transplantation
Nutrition and chronic renal disease

Hematologic Diseases

Anemias of genetic origin
Nutritional anemias
Metabolic disorders of iron transport and storage
Disorders of blood cell production
Hematopoietic tissue transplantation immunology
Autoimmune hematologic diseases
Iron chelation therapy

The Institute's programs are of profound importance to the American people since no subgroup of our population is immune to attack by one or more of the diseases or disorders that the NIADDK addresses.

The impact of some of these diseases is indicated in exhibit 2, which shows the prevalence, or number of affected individuals in the United States, and the approximate economic costs to the American public. The collective economic burden of the diseases addressed by this Institute exceeds $100 billion annually. The more profound costs of chronic disease, in terms of human suffering, cannot easily be measured, but they are no less significant. Finding effective methods to prevent, control, and treat these diseases and disorders, through its various research programs and activities, is the mission of the NIADDK.

EXHIBIT 2. Prevalence and economic costs of selected disease groups

	Prevalence (in millions)	Economic Cost[1] (in billions)
Arthritis and Related Diseases	$37.0	$18.6[2]
Diabetes	11.0	10.8[2]
Digestive Diseases	38.0	50.0[2]
Kidney and Urologic Diseases	13.0	5.5[3]

[1] *Including direct costs for hospital care, professional services, and drugs as well as indirect costs of productivity lost because of death and disability.*

[2] *As reported by the national commissions on arthritis, diabetes, and digestive diseases, respectively. In the case of digestive diseases, the National Digestive Diseases Advisory Board estimates an economic cost of $50 billion in annual lost wages, taxes, disability, and health care payments, and $17 billion in direct health care costs.*

[3] *Direct medical cost of kidney disease only. (Source: National Kidney Foundation)*

Organization of the Institute

As the NIADDK moves forward in pursuit of the knowledge that will lead to more effective methods for improving the health of the American public, its organization must rely on coordinated, interacting mechanisms that will produce responsive and substantive information. The current system under which the NIADDK operates is designed to meet these essential requirements.

The organizational structure of the NIADDK (exhibit 3) reflects its emphasis on basic biomedical and clinical research and research training. Institute efforts are planned and coordinated through both an extramural support program, which provides funding for research at universities, clinical facilities, and research institutions across the country and abroad, and an intramural component, which focuses on research conducted primarily within the NIADDK's laboratories and clinical facilities on the NIH campus and in Arizona.

The administrative and advisory activities of the Institute are organized to provide programmatic guidance and fiscal, analytical, and review services to facilitate the research efforts. Activities aimed at developing and sustaining linkages to the scientific and health-care community also fall within the Institute's realm of administrative and advisory functions.

Office of the Director

The focal point for managing NIADDK operations is the Office of the Director. Because this office has ultimate responsibility for the research sponsored and the results disseminated by the Institute, the Director and staff are involved in planning and coordinating the various activities of each of the NIADDK's programs.

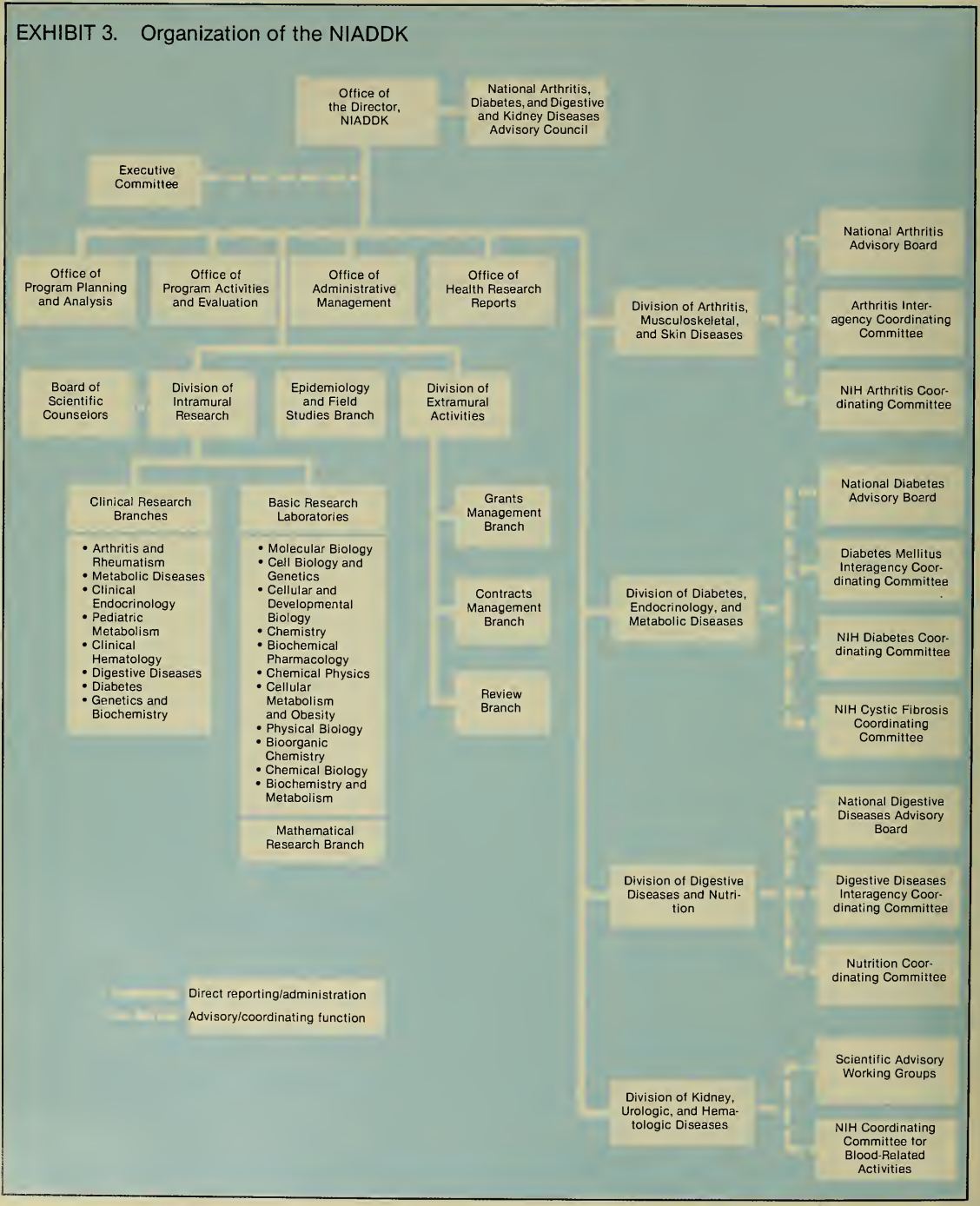
Specifically, the Director's office provides policy direction and staff guidance and oversees the preparation of plans and reports in such areas as scientific program planning, administrative management, and utilization of resources. In addition, the Office of the Director is directly responsible for developing the NIADDK's annual budget, which reflects funding needs and resource priorities for all activities—both program-related and administrative.

The Office of the Director coordinates and prepares information to describe the NIADDK's program progress and future plans to the Director of NIH and to Congress. These are ongoing activities that are mandated by the Institute's authorizing legislation so that progress achieved and problems encountered can be continually assessed.

The Office of the Director is assisted in its responsibilities by the following offices and program components:

- *Office of Administrative Management*—responsible for planning, coordinating, and directing management of day-to-day operations, including budget and financial management, personnel, and office services.
- *Office of Program Planning and Analysis*—responsible for Institute activities in the areas of planning, program and policy analysis, and legislation; analyzes Institute programs and develops

EXHIBIT 3. Organization of the NIADDK



Institute analytic capabilities and data base for planning, policy formulation, and budget justifications; and oversees Institute congressional activities having policy implications.

- *Office of Program Activities and Evaluation*—responsible for the evaluation of Institute program activities; responsible for coordination, review, and presentation of Institute activities related to disease prevention; and coordinates medical technology assessment and technology transfer activities of the Institute.
- *Office of Health Research Reports*—coordinates preparation and distribution of information and publications on the Institute's programs and activities to a variety of audiences, responds to public inquiries in areas relating to disease categories encompassed by the Institute's mission, and advises Institute staff on matters relating to the Freedom of Information Act.
- *Extramural Divisions*—provide oversight and management of all aspects of research and training programs and projects conducted off-campus as follows:
  - —*Four extramural research Divisions* coordinate and direct scientific planning, monitoring, and reporting of research and training programs in their respective research areas, in close cooperation with the Office of the Director.
  - —*The Division of Extramural Activities* provides fiscal management of extramural research awards, reviews applications and proposals for specialized research projects, and assures operational coordination among the extramural research programs.
- *Division of Intramural Research*—through intramural laboratory and branch chiefs, plans, coordinates, and conducts research activities in the Institute's laboratories and clinical facilities.

These organizational components provide the substantive input that the Office of the Director requires to develop program plans and policies that are responsive to the Institute's long-term goals and objectives as well as to specific requests for information or studies, originating in Congress or elsewhere in the Executive Branch. The Director's office also relies on the expertise and advice provided by the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council, a senior consultative body whose guidance is important to the Institute's program organization and operations, by the national advisory boards and coordinating groups described below, and by a newly created Executive Committee, composed of intramural and extramural senior staff members.

Extramural Activities

The extramural program supports investigations that are funded by the Institute but conducted at universities, private and public research facilities, and hospital-based clinical research centers throughout the Nation and, in certain cases, in other countries. The NIADDK uses grants, contracts, and various other funding mechanisms to generate and administer the extramural project activities of the four research Divisions. The various award mechanisms are described in exhibit 4.

The primary mechanism of support of research by the NIADDK is through investigator-initiated research project grants, because this is the best way to advance the base of scientific knowledge.

Each NIADDK Division functions as a distinct administrative unit with responsibility for allocating and managing research funds through research grants, contracts, fellowships, training grants, and special awards to qualified applicants and institutions. Supported activities range from basic and applied research investigations (including clinical studies) to training programs in fundamental and clinical sciences.

In keeping with the needs, priorities, and research requirements of the disease areas under the purview of the Institute, there is strong emphasis on the support of basic research. This emphasis is particularly important because the etiologies of many of the major diseases involved are unknown. A significant proportion of extramural research support is aimed at clinical studies, to provide an optimal mix for rapid advances in treating the various diseases studied by the NIADDK.

The testing for safety and efficacy of an emerging technique, drug, device, or procedure is generally accomplished through clinical studies and trials. Examples of such studies currently or recently supported include the following:

- Total lymphoid irradiation in rheumatoid arthritis.
- Diabetes Control and Complications Trial.
- The National Cooperative Gallstone Study.
- The healing rate of scleroderma esophagitis.
- Collaborative study of adult glomerular disease.

The Institute's extramural program funds and coordinates each trial over its full course, which may be several years. Population samples for a particular clinical trial may be several thousand people across the Nation or a few hundred residents in a single community. Clinical trial results provide valuable information concerning the advisability of using the subject drug, device, or procedure in the health-care setting.

EXHIBIT 4. NIADDK extramural program award mechanisms

- Development contracts. These contracts, which are relatively rarely used, are awarded for projects to produce substances, devices, systems, or other approaches to diagnose, prevent, treat, or control diseases. Examples of such projects include the development of effective vaccines or drugs, surgical techniques or medical devices to assist or replace organ functions, and sophisticated instruments to refine laboratory or clinical procedures.

- Demonstration contracts. These contracts are awarded to support projects designed to demonstrate the feasibility of applying biomedical research advances or technologies to individual or community situations to solve certain health problems.

- Research and development support. Awards in the research and development category are offered to finance certain resources or services to aid ongoing activities. These include data processing, drug testing, toxicology screening, logistics services, and collection and distribution of materials needed to conduct biomedical research and development.

- Scientific communication and evaluation awards. These awards are provided to support special conferences, workshops, and seminars that are planned to analyze the significance of new biomedical research findings and for developing a scientific consensus on those findings.

- Manpower training awards. A detailed description of the mechanisms used by the Institute to support manpower development is provided under "Research Manpower Development" in this chapter.

- Exploratory grants. These grants support planning for new programs, expansion or modification of existing resources, and feasibility studies to explore various approaches to the development of interdisciplinary programs that offer potential solutions to problems of special significance to the mission of the Institute. Such exploratory studies may lead to specialized or comprehensive centers.

- Small business innovation research grants, phase I. These grants support projects, limited in time and amount, to establish the technical merit and feasibility of research and development ideas that ultimately may lead to commercial products or services. These awards may be made only to small businesses.

- Research project grants. An institution is awarded a grant on behalf of a principal investigator to facilitate pursuit of a scientific initiative or objective in the area of the investigator's interest and competence. Applications are accepted for health-related research and development in all areas within the scope of the Institute's mission. This is the largest single support mechanism utilized by NIADDK.

- Program project grants. Program project grants are awarded to an institution on behalf of a principal investigator for the support of a broad-based, often multidisciplinary, long-term research program with a particular major objective or theme. The type of project supported with this award involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. Each project supported under a program project grant is expected to contribute to the overall program objective.

- Center grants. Center grants are awarded to institutions on behalf of a program director and group of collaborating investigators to provide support for long-term, multidisciplinary programs of research and development. However, center grants are more likely to have a clinical orientation than are program project grants and are usually developed in response to announcements of specific program needs and requirements of the Institute.

- Resource awards. These awards provide support for research resources such as computer centers or general clinical research centers operating on an institutional, regional, or national basis. While the resources normally serve a wide range of biomedical research, they may be oriented toward specific research needs.

- Conference grants. Conferences planned for the purpose of coordinating, exchanging, and disseminating scientific research information related to the Institute's program interests may be supported by conference grants. Generally, the awards are provided for cooperative participation with other organizations in the support of conferences rather than for provision of sole support.

- Research contracts. Contracts are offered for specific research problems that have been identified by the Institute and that require central direction, control, and management. Clinical trials of new or established therapies may be funded by this mechanism.

Intramural Research

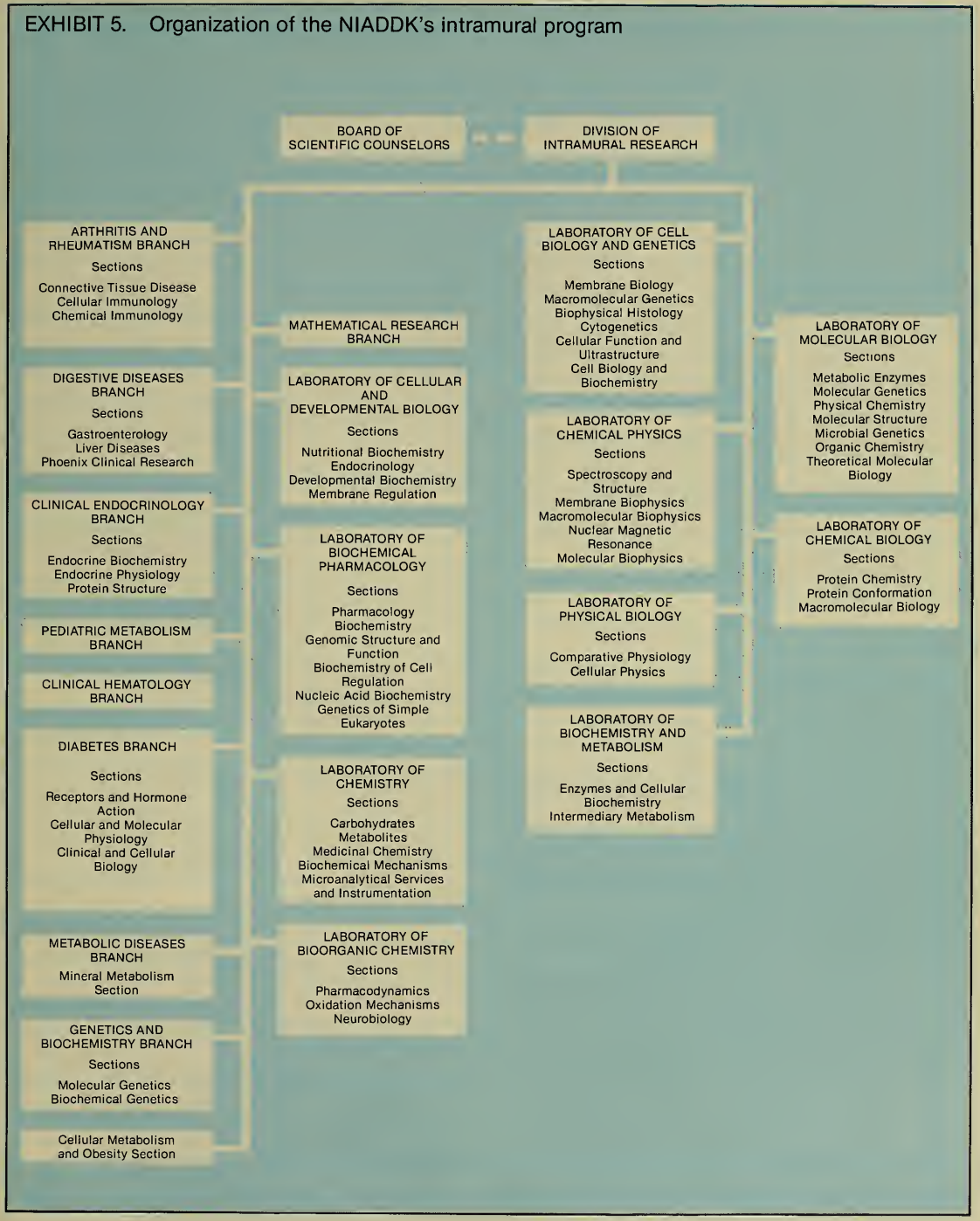
The Division of Intramural Research covers investigations within the Institute's laboratory and clinical facilities in Bethesda and Phoenix. Intramural research activities are conducted by eight branches engaged primarily in clinical research on arthritis and rheumatic diseases, metabolism, endocrinology, hematology, digestive diseases, diabetes, and genetics; a ninth branch addresses theoretical mathematical modeling of biological problems. In addition, there are 10 laboratories with component sections organized by scientific disciplines (e.g., molecular biology, chemistry, pathology, pharmacology, physics, and biochemistry). The laboratories are engaged primarily in fundamental research that is related to the Institute's diverse areas of responsibility. The organization of the intramural laboratories and branches is shown in exhibit 5.

A related intramural group, the Epidemiology and Field Studies Branch, develops and applies epidemiologic methods in field studies among selected populations at risk of developing specific diseases. Investigators in the Epidemiology and Field Studies Branch conduct research throughout the United States and provide assistance to numerous investigators engaged in research on arthritis and metabolic disorders.

Monitoring and advice on intramural program direction and administrative activities are provided by the Board of Scientific Counselors, an internal review committee. Close collaboration with scientists of other NIH Institutes, other government agencies, and investigators in institutions throughout the United States and abroad ensures an effective approach to research strategy. Moreover, because the intramural program constitutes such an important component of the NIADDK's activities and responsibilities, its ongoing and planned research efforts are given strong consideration in program planning by the Institute's other organizational units.

The intramural research staff of the NIADDK is generally acknowledged to be a highly productive and innovative group of scientists. The unusual caliber of this program is reflected in the several Nobel prizes and other prestigious awards that have resulted from its work. Also, many scientists who trained in the intramural research program of the Institute are now prominent faculty members at universities throughout

EXHIBIT 5. Organization of the NIADDK's intramural program



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National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIH
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* Expiration of term

the country. The various laboratories and clinical branches are universally sought after for scientific collaboration, while the mathematics branch serves as a major resource for the intramural efforts of the NIADDK and other NIH Institutes alike. The NIADDK is justly proud of the achievements and reputation of its intramural research program.

Advisory and Coordinating Groups

Over the years, the NIADDK's responsibilities and programs have been greatly influenced by the rapid evolution of biomedical research advances and technology, future research opportunities, and the public's demands for more and better health-care services. To keep pace with the rapidly developing biomedical research environment and to ensure that the NIADDK's numerous programs continue to address appropriately the Nation's health needs, the Institute relies heavily on guidance and recommendations provided by various advisory and coordinating groups. Each of these important bodies contributes to the direction, coordination, and evaluation of research and training activities in major disease areas.

National Advisory Council

The National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council is one of the national advisory councils established legislatively for the NIH, each an important adjunct to its respective Institute. The NIADDK's Advisory Council is composed of eminent experts in selected areas of biomedical research; civic leaders, educators, and laypersons with interest in a particular disease or field of research in that disease; and representatives from the Department of Defense and the Veterans Administration. Current members of the group are listed on the following pages.

The functions and responsibilities of the National Advisory Council are primarily to assist the Office of the Director in overseeing the activities of the Institute, provide advice and counsel with regard to the In-

stitute's goals and programs, and review and approve or disapprove extramural research grant requests, after they have undergone a primary peer review for scientific merit and feasibility. The Council is charged with assuring that the extramural research projects supported by the NIADDK have a sound scientific basis, are relevant to the Institute's programs, and show promise of achieving results. The Council's involvement in the planning and coordination of programs within the Institute provides it with an appropriate perspective for judging the merits of grant applications in light of the NIADDK's overall priorities for new research.

Members of the National Advisory Council are grouped into four subcommittees, one for each of the four research Divisions that constitute the extramural research program; they are assigned to the subcommittee most appropriate to their special scientific, education, or public affairs expertise in a particular disease area. Each subcommittee is responsible for reviewing the substance of the extramural grant applications for research and training projects related to the diagnosis, prevention, and treatment of the diseases in its assigned area. Its recommendations on these grants and training awards are then presented to the full Advisory Council for further consideration and final approval. The subcommittees also review and evaluate the overall administrative activities of their respective Divisions and suggest changes in program structure and operations when they deem such changes necessary.

National Advisory Boards

Among the many recommendations in the plans submitted by the national commissions on arthritis, diabetes, and digestive diseases was the establishment of national advisory boards for each disease area. When formally designated, each of these boards was authorized by Federal law to monitor and facilitate the research, training, prevention, and control programs within its area of interest.

The National Arthritis Advisory Board, National Diabetes Advisory Board, and National Digestive Diseases Advisory Board are composed of members representing a variety of scientific, educational, health-care, and public-service disciplines. Current members of the boards are listed on the following pages.

The primary functions of each board are to review and evaluate progress of the long-range plan developed for its respective disease area; update the plan to assure its continuing relevance to public health needs; provide advice and recommendations on plan implementation to the Directors of the NIADDK and the NIH, the Secretary of Health and Human Services (HHS), and other Federal agencies; and maintain liaison with advisory bodies of other Federal agencies involved in implementing the plan.

To keep Congress informed of all ongoing activities, issues, and anticipated needs in their disease areas, the advisory boards are required by law to submit annual reports of their activities along with recommendations for any appropriate changes in the plans.

Interagency Coordinating Committees

The NIADDK participates in interagency cooperation through three interagency coordinating committees, which are specifically responsible for fostering and

National Arthritis Advisory Board

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Massachusetts General Hospital
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Joan D. Sutton, R.N., M.S.N.
Johns Hopkins University
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Francis S. Symms
Alexandria, Virginia

Eng Meng Tan, M.D.
Scripps Clinic and Research Foundation
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Malcolm Grow Medical Center
Andrews Air Force Base
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David Wayne Smith, Ph.D.
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National Diabetes Advisory Board

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Nina Berlin
Pennsylvania Task Force on Diabetes
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Baltimore, Maryland

Matthew D. Davis, M.D.
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Madison, Wisconsin

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Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Leatrice Ducat
Narberth, Pennsylvania

Daniel Foster, M.D.
University of Texas
Dallas, Texas

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Benjamin Greenspoon
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Caroline S. Lurie
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Wendell Mayes, Jr.
Independence Broadcasting Company
Austin, Texas

Arthur Raymond
University of North Dakota
Grand Forks, North Dakota

Gerald M. Reaven, M.D.
Stanford University
Stanford, California

Gayle E. Reiber, R.N.
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National Digestive Diseases Advisory Board

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University of Texas
Dallas, Texas

John C. Daly
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Irving A. Rubin
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Chapel Hill, North Carolina

Harry Tamoney, Jr., M.D.
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improving research and health-care programs in the areas of arthritis, diabetes mellitus, and digestive diseases. The legislatively mandated interagency committees serve to facilitate communication among all Federal agencies directly or indirectly involved in the three disease areas. Since their establishment in the mid-1970's, these committees have worked closely with the national commissions and advisory boards to develop improved approaches to information exchange, joint planning, and the identification of promising areas for cooperation.

The membership of each interagency coordinating committee includes the director of the relevant NIADDK Division, who serves as chairman, and representatives from selected Institutes within the NIH and from other Federal departments and agencies with related functions and activities. Through these committees, the Institute is able to determine whether programs of research, health care, and related social services are adequate to meet the needs of those afflicted with arthritic disorders, diabetes, and digestive diseases.

Trans-NIH Coordinating Committees

Certain complex health issues or problems span the program interests of several Institutes, thereby requiring collaborative effort to assure program balance and minimize duplication of activity. For such trans-NIH issues, the Director of the NIH has appointed coordinating committees to provide a forum for exchange of information, a mechanism for the coordination of individual programs, and a focus for policy development. The coordinating committees are composed of representatives of all the appropriate Bureaus, Institutes, and Divisions (BID's) within the NIH. Their activities foster the continuing development of new research approaches in the participating NIH components, and the committee chairman serves as a principal advisor to and representative of the Director, NIH, on all matters relating to that area. The following sections describe coordination efforts in several trans-NIH areas in which the NIADDK plays a major role.

Arthritis. The NIH Arthritis Coordinating Committee (ACC) includes representatives from each of the BID's having research interests in one or more aspects of the rheumatic diseases. The activities of the ACC (chaired by the NIADDK representative) are meant to complement those of the Arthritis Interagency Coordinating Committee (AICC) created by the National Arthritis Act. The committee is concerned with:

- Strengthening the NIH system for reporting on arthritis research and coordinating these efforts with other Federal agencies.
- Identifying opportunities for joint sponsorship of workshops and symposia in selected areas of arthritis research.
- Providing a focus to stimulate and coordinate research in this area.
- Exploring opportunities to share facilities and other resources for arthritis research.

Planning and emphasis are based on the missions, interests, and research program plans of the participating BID's, as well as on recommendations originally posed by the National Commission on Arthritis and Related Musculoskeletal Diseases. Coordination among the NIH components has been achieved through joint program announcements, workshops, and conferences.

The committee had a planning role in a program for establishing comprehensive regional centers for children with rheumatic diseases; the centers were organized under the Office of Maternal and Child Health. The six centers funded to date will include patient care and management, education of the family and of health professionals, and involvement in community programs of Federal, state, and local origin. In addition, the committee took an active interest in a conference on local bone growth factors sponsored by the NIADDK and the National Institute of Dental Research.

Diabetes. Because diabetes affects so many body systems, research programs in this area fall within the scope of almost all of the BID's. Thus, the trans-NIH Diabetes Research Program was established to promote cooperation in diabetes-related programs among all of the relevant Institutes at the NIH. Activities have included joint program announcements and requests for applications, as well as cooperation in fostering research manpower development programs.

During the past year, the following activities have been initiated under the auspices of the trans-NIH diabetes program:

- The fifth annual report of the National Diabetes Advisory Board, which highlights various new opportunities for research in diabetes-related areas, was distributed to every NIH grantee with a diabetes-related project.
- Several NIH Institutes participated in a Workshop on Immunosuppression in the Management of IDDM (insulin-dependent diabetes mellitus) in order to assess the current state of the art in this rapidly emerging area of research interest.

- The NIADDK, the National Institute of Allergy and Infectious Diseases, and the National Institute of Child Health and Human Development cosponsored a Request for Applications on the Immunobiology of IDDM.
- Several NIH Institutes collaborated in supporting the development of new mechanisms for the procurement and distribution of human tissues for biomedical research through the National Diabetes Research Interchange.
- Several NIH Institutes participated in a workshop on glycosylated proteins, organized by the NIADDK's National Diabetes Data Group, to assess and compare new analytical methodologies and to consider issues related to standardization of techniques.
- Several NIH Institutes collaborated in the planning and implementation of the Diabetes Control and Complications Trial in conjunction with various organizations in the private sector.
- Several NIH Institutes cosponsored a national conference for Federal health-care professionals on the prevention and treatment of five complications of diabetes, in conjunction with other concerned Federal agencies.

Participants in the trans-NIH diabetes program also collaborate with the NIADDK's National Diabetes Data Group. The data group serves as the central point within the NIH for the collection, analysis, and evaluation of epidemiological data that are fundamental to the development of sound scientific and public health policies related to diabetes and its complications. Members of the trans-NIH diabetes program also utilize the NIADDK's National Diabetes Information Clearinghouse, the national reference source for information on professional and patient education materials and programs related to diabetes and its complications.

Nutrition. The NIH is the primary Federal agency that conducts and sponsors research and training in nutrition as it relates to health maintenance, human development, and disease prevention and treatment. The NIH Nutrition Research Program involves all of the NIH's BID's that support nutrition-related research and is coordinated through its Nutrition Coordinating Committee (NCC). The NCC not only minimizes duplication of effort among the NIH components, but also identifies areas in which research and research manpower in nutrition require further nurturing. Program announcements and requests for applications developed by the NCC and sponsored by more than one BID encourage activity in areas of perceived need in nutrition.

The NCC has developed a master nutrition plan and prepares an annual report, "Program in Biomedical and Behavioral Nutrition Research and Training," that emphasizes research in four critical areas: clinical nutrition throughout the life cycle, the role of nutrition in disease development, prevention of disease, and treatment of disease. In addition to identifying research priorities, the nutrition plan emphasizes the transfer of modern nutrition technology and nutrition education for professionals and the public.

The NIADDK's involvement in the NCC has included the full range of NCC activities, but has focused particularly on several of immediate Institute concern: evaluation of the Clinical Nutrition Research Units, with the National Cancer Institute; preparation of a program announcement on overnutrition and obesity, with seven NIH Institutes; participation on a planning committee on problem areas in the support of nutrition work; preparation of data, analyses, and textual information concerning the NIADDK programs in specific areas of nutrition; and the planning of a workshop on nutrition and hypertension.

Cystic fibrosis. The Cystic Fibrosis Coordinating Committee was established to serve as a focus for the coordination of NIH support of research and research training related to cystic fibrosis. The committee is cochaired by representatives of the NIADDK and the NHLBI and includes members from each of those BID's with responsibilities relating to cystic fibrosis. Specific functions of the committee include cataloging NIH activities and support related to cystic fibrosis, coordinating and facilitating program initiatives in the BID's to address the needs and opportunities in research relevant to cystic fibrosis, encouraging trans-NIH collaboration on activities related to cystic fibrosis, and serving as an information resource and point of contact with other agencies and organizations regarding advances and opportunities in cystic fibrosis research and research training.

Blood-related activities. Support and management of blood-related research activities are shared among several Institutes of the NIH. The NIH Coordinating Committee for Blood-Related Activities coordinates the overall course of investigations dealing with blood and the use of blood resources. The membership of the coordinating committee represents six Institutes at the NIH, including the NIADDK, as well as the Division of Research Resources and the NIH Clinical Center. One of the major goals of the committee is the preparation of a directory of blood-related research projects conducted and supported by the NIH, other agencies of the Federal Government, and nongovernment organizations.

Board of Scientific Counselors

The NIADDK's Board of Scientific Counselors was initiated in 1956 and currently operates under the statutory authority of Section 222 of the Public Health

Service Act (P.L. 87-838, Public Health Service Amendments of 1962), serving as an internal review committee responsible for monitoring the activities of the Institute's intramural research program. The operations of the Board are governed by the Federal Advisory Committee Act, P.L. 92-463. The formation of the Board was considered essential to ensure unbiased, extra-Governmental expert review of intramural research activities. The activities of the Board developed in parallel with the review mechanisms established for the extramural research program.

The Board (whose members are listed below) is composed of individuals eminent in research fields and scientific disciplines related to the basic and clinical research activities of the Institute. Board members meet twice a year to visit Institute laboratory facilities, review scientific progress, and make recommendations for the program to the Director of the Division of Intramural Research, the Director of the NIADDK, and the Director of the NIH. In addition, the Board is required to submit an annual report on findings to the Secretary of HHS, the Assistant Secretary for Health, and the Director of the NIH.

Board of Scientific Counselors

CHAIRMAN
Robert E. Canfield, M.D. (1985)*
Columbia University
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Rockefeller University
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Washington University
St. Louis, Missouri

Marian E. Koshland, M.D. (1985)
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Berkeley, California

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New York, New York

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Rahway, New Jersey

Executive Secretary
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Bethesda, Maryland

* Expiration of term

Special Programs

Given the Institute's varied responsibilities, the opportunities for fostering collaboration among scientists across the Nation and around the world are numerous. Over the years, the NIADDK has implemented special programs to expand research opportunities and services, going beyond the laboratory to the community where those afflicted with disease and those who treat them may benefit more quickly.

NIADDK's Research Centers Programs

In addition to providing support to institutions and organizations for the traditional research and research training programs, the Institute also has responsibility for a program of center facilities. Through the centers programs, some of which were specifically authorized by legislation in the mid-1970's, institutions have been competitively selected to provide a variety of multidisciplinary approaches to research, education, and community demonstrations in arthritis and related musculoskeletal diseases, diabetes, endocrine and metabolic disorders, digestive diseases and nutrition-related problems, and specialized research into kidney and urologic disorders.

The NIADDK sponsors 20 Multipurpose Arthritis Centers (MAC's) across the country. The MAC's are engaged in activities that address all phases of the arthritis problem, from basic research in the causes of the disease and pilot and feasibility studies for developing investigators to education and training and the community application of evolving methods of treatment.

The Diabetes Centers Program consists of two types of facilities: Diabetes-Endocrinology Research Centers (DERC's), which concentrate on basic and clinical investigations conducted in a core setting of shared, comprehensive laboratory facilities, and the Diabetes Research and Training Centers (DRTC's), which encompass basic and clinical research as well as the education and training of new investigators and the translation of research results into improved care and management of diabetic patients. For added research incentive, both DERC's and DRTC's provide limited funds for pilot or feasibility studies to encourage young investigators and promote innovation in research concepts.

The Division of Digestive Diseases and Nutrition sponsors centers that support and conduct basic and clinical investigations of a variety of health problems related to its program areas. Two such centers conduct research on liver disease and the effect of drugs and injuries on the liver. Another center is studying diet and eating behavior that contributes to obesity, a model program that is intended to foster multidisciplinary research and exchange of information. Still another focuses on peptic ulcer. The Institute is also currently supporting five Clinical Nutrition Research Units, which serve as focal points for multidisciplinary research in clinical nutrition as well as provide for the development of programs in clinical nutrition that enhance the education of various health professionals.

Activities of the various types of centers differ according to local need and support of research, clinical, educational, training, and demonstration projects. All centers, however, operate in a core setting of shared,

comprehensive facilities, resources, and trained investigators to promote research and the translation of research results into improved patient care.

The geographic distribution of the NIADDK-supported centers is shown in exhibit 6. Details of organization and activities in the various types of centers are presented under "Special Programs" in chapters II through V.

The multipurpose centers program provides important linkages among the NIADDK, the scientific community, and the health-care delivery system, and continued evaluation is essential to maintaining those linkages. Current evaluation reports for the Multipurpose Arthritis Centers and the Diabetes Research and Training Centers are provided in chapter VI.

A Program for International Cooperation

The NIADDK has supported a number of international collaborative and individual research efforts that draw upon the talents and investigative expertise of the international scientific community. Continued collaboration with international scientists and the funding of projects that may have worldwide impact is an ongoing priority for the Institute. Through the Bilateral Cooperative Agreements Program, the NIADDK has developed collaborative and cooperative activities with Japan, the U.S.S.R., and France, in several important fields.

U.S.-Japan cooperative program in malnutrition. Since 1966, the U.S.-Japan Cooperative Medical Sciences Program has been actively engaged in collaborative research efforts to develop greater understanding of the effects of malnutrition on physical growth, mental development, and performance. These activities and projects are carried out through cooperative arrangements developed between the United States and Japan, which share responsibility for the program.

Research continues to be the primary focus of activities supported by the malnutrition program panel. Studies have been developed and conducted abroad among populations with severe nutritional deficiency diseases and are designed to find solutions to complex malnutrition problems. The availability of large population groups afflicted with nutrition disorders provides the NIADDK and the other sponsoring members of this program with valuable information and insight into the many aspects of malnutrition and its implications for health and well-being.

U.S.-U.S.S.R. cooperative program in arthritis. The origins of the U.S.-U.S.S.R. arthritis program can be traced to the Health Exchange Program of 1972, a joint agreement developed to improve collaboration in the field of public health and medical science. In September 1973, arthritis became the fourth major cooperative project in the health sciences under this program. The program is organized into three major areas—clinical studies in rheumatic disease, the basic science of rheumatic disease, and orthopedic surgery for arthritis—with emphasis on clinical studies using commonly agreed-upon protocols for the treatment of rheumatoid arthritis and systemic lupus erythematosus. Twelve major meetings have been held between the members of the cooperating research centers, featuring discussions of preliminary study results and future projects and supplemented by the exchange of reprints and lecture materials. Scientists from both countries have been invited to visit and work in their collaborators' laboratories and to participate in various symposia and professional society meetings as well.

NIH-INSERM agreement. Under an agreement program between the NIH and the National Institute of Health and Medical Research of France (INSERM), substantial scientific collaboration has been fostered between the Clinical Endocrinology Branch, the NIADDK, and the Unité de Recherche sur la Glande Thyroide et la Régulation Hormonale, INSERM. The exchange of scientists from both groups has provided excellent opportunities for collaborative research and effective use of trained personnel in the study of thyroid hormone synthesis and metabolism. Investigators from both countries had been working on different but related aspects of thyroid physiology and biochemistry. Through a melding of the programs available to each group, research progress in these areas has been greatly advanced, and new procedures to resolve problems in thyroid function have evolved. In addition, many scientific papers have been published jointly.

Visiting scientists program. The NIADDK intramural research program sponsors researchers from many countries under its visiting scientists program, and in return, intramural investigators from the Institute visit and collaborate with scientists in laboratories and clinics abroad. During the past year, researchers from Israel, India, Poland, Japan, China, the United Kingdom, France, Germany, and other countries have worked in the intramural laboratories and clinics of the NIADDK. The exchange of high-caliber scientists across national boundaries promotes cross-fertilization of ideas and techniques; it has proven mutually beneficial for many years and is expected to provide significant scientific dividends in the future.

Extramural research in other countries. To capitalize on the expertise of investigators in other countries and to further the progress of research in high-priority health problems of international scope, the NIADDK continues to support investigator-initiated research by scientists outside the United States as part of its extramural research programs. Support is provided through grants and contracts for highly qualified investigators conducting the following types of studies:

EXHIBIT 6. The NIADDK centers grant program

▲ **MULTIPURPOSE ARTHRITIS CENTERS**

University of Alabama School of Medicine, Birmingham, Ala.
University of Arizona College of Medicine, Tucson, Ariz.
University of California School of Medicine, San Francisco, Calif.
Stanford University School of Medicine, Stanford, Calif.
University of Colorado Health Sciences Center, Denver, Colo.
University of Connecticut School of Medicine, Farmington, Conn.
Indiana University School of Medicine, Indianapolis, Ind.
Johns Hopkins School of Medicine, Baltimore, Md.
Boston University School of Medicine, Boston, Mass.
Brigham and Women's Hospital, Boston, Mass.
University of Michigan Medical School, Ann Arbor, Mich.
University of Missouri Medical Center, Columbia, Mo.
Washington University School of Medicine, St. Louis, Mo.
Dartmouth Medical School, Department of Medicine, Hanover, N.H.
State University of New York, Downstate Medical Center, Brooklyn, N.Y.
University of North Carolina Medical Center, Chapel Hill, N.C.
University of Cincinnati Medical Center, Cincinnati, Ohio
Case Western Reserve University, Cleveland, Ohio
Vanderbilt University Medical Center, Nashville, Tenn.
Medical College of Wisconsin, Milwaukee, Wis.

● **DIABETES RESEARCH AND TRAINING CENTERS**

University of Chicago, Chicago, Ill.
Indiana University, Indianapolis, Ind.
University of Michigan, Ann Arbor, Mich.
Washington University, St. Louis, Mo.
Albert Einstein College of Medicine, New York, N.Y.
Vanderbilt University, Nashville, Tenn.
University of Virginia, Charlottesville, Va.

○ **DIABETES-ENDOCRINOLOGY RESEARCH CENTERS**

University of Iowa, Iowa City, Ia.
University of Pennsylvania, Philadelphia, Pa.
Baylor College of Medicine, Houston, Tex.
University of Washington, Seattle, Wash.
University of Massachusetts, Worcester, Mass.

△ **OTHER SPECIALIZED CENTERS**

Clinical Nutrition Research Units—
Georgia Medical College, Augusta, Ga.
University of Chicago, Chicago, Ill.
Columbia University, New York, N.Y.
Vanderbilt University, Nashville, Tenn.
University of Wisconsin, Madison, Wis.
Peptic Ulcer Center—
University of California, Los Angeles, Calif.
Liver Center—
University of California, San Francisco, Calif.
Hepatitis-Cirrhosis Center—
Albert Einstein College of Medicine, New York, N.Y.
Obesity Center—
St. Luke's Hospital Center, New York, N.Y.

- Action of hormone receptors in the cell membrane.
- Biochemical studies on basement membrane in diabetes.
- Kidney graft rejection.
- Protein, fat, carbohydrate, and salt metabolism during continuous ambulatory peritoneal dialysis for chronic renal failure.
- Medical versus surgical treatment of vesicoureteral reflux (from the bladder back into the ureters) in children.
- Steroid receptors in benign prostatic hyperplasia (BPH, or prostate enlargement).
- Thalassemias, hemoglobinopathies, and related problems of abnormal hemoglobins.

Conferences, seminars, and meetings. Scientific meetings with international audiences play a major role in scientific communication because they provide a forum for the exchange of research information among investigators from different countries, and they often stimulate further scientific collaboration. The NIADDK continues to support selected international conferences and symposia as part of its programs; for example, last

year the NIADDK provided support to 17 such meetings addressing topics such as genetics, nutrition, diabetes, osteoporosis, and many basic science issues.

Research Manpower Development

In the 33 years since its establishment, the NIADDK has made impressive strides in biomedical research. Maintaining that momentum requires a complex interplay of factors, including the availability of basic scientific knowledge and technologic methods, the availability and appropriate utilization of trained investigators, and financial support. While the lack of any single resource may impede scientific progress, the need for trained personnel is particularly critical. The development of research manpower is crucial to the accomplishment of the NIADDK's goals and has been a high Institute priority.

Through ongoing analysis and evaluation of program needs and maintenance of a wide range of training mechanisms, the NIADDK continues to seek motivated future investigators to meet critical needs. Recently initiated training mechanisms, such as the Clinical Investigator Award, the National Research Service Award Senior Postdoctoral Fellowship, and the Special Emphasis Research Career Award, as well as the New Investigator Research Award, contribute markedly to Institute efforts to attract and prepare outstanding investigators for research careers. The new Physician Scientist Award (see below) is expected to provide one of the most effective mechanisms available to help reach this goal. Exhibit 7 describes the mechanisms utilized by the NIADDK to supply talented scientists for each of its categorical disease research programs.

Vigorous efforts have been made to avert shortages of personnel in vital areas. However, there are still declining numbers of physicians who pursue research careers and a shortage of trained epidemiologists in many important fields.

Physician Researchers

In an effort to attract more physicians to academic research careers, the NIADDK promotes short-term training programs for students in professional schools. During summer breaks, students are given the opportunity to gain research experience and be exposed to the rewards of a research career at a formative stage of their professional training. Once they have received their professional degrees, such students are eligible for grants in individual or institutional postdoctoral training programs, and those with demonstrated dedication and aptitude in research are eligible for the Clinical Investigator Award, the Research Career Development Award, the Special Emphasis Research Career Award, and the newly developed Physician Scientist Award. By continuing to support physicians throughout the various stages of lengthy research training, the NIADDK can help to ensure that adequate numbers of physician researchers will be available to address the Institute's research concerns from both basic and clinical perspectives.

Other Research Professionals

Often, critical manpower needs arise in specific areas or disciplines. For example, progress in epidemiologic studies has been severely restricted because the number of professionals trained in pertinent fields is insufficient. To correct this deficiency, the NIADDK encourages the formal training of epidemiologists in field and survey methods through university-based degree programs, nondegree programs in the arthritis and diabetes centers, and epidemiologic projects at the Centers for Disease Control, the National Center for Health Statistics, the Veterans Administration, and the NIADDK field studies units. Recognizing the importance of epidemiologic studies to comprehensive national research efforts, the NIADDK established an arthritis epidemiology program office in 1978 to encourage research in rheumatic diseases and, with seven other Institutes, solicited applications for diabetes epidemiology research and training.

By marshalling all available resources and coordinating them efficiently, the NIADDK hopes to moderate or avert the severe shortages of trained personnel anticipated in coming years.

Minority Program Support

Traditionally, ethnic and racial minorities and women have been underrepresented in the mainstream of biomedical research, but the Nation cannot afford to allow such human resources to remain untapped. Therefore, the NIADDK vigorously supports programs to strengthen research capabilities and enlarge the potential investigator pool in colleges and universities attended largely by women and minority groups.

In 1977, the NIADDK participated in the initiation of the NIH Extramural Associates Program to familiarize minority and women's educational institutions with NIH research activities, thus enhancing their capabilities to participate in NIH-supported health research. Through the Minority Biomedical Research Support Program of the Division of Research Resources, the NIADDK funds projects designed to improve the biomedical science capabilities of minority institutions through support of undergraduate students

EXHIBIT 7. NIADDK research manpower development mechanisms

- **NATIONAL RESEARCH SERVICE AWARDS (NRSA).** These awards provide for the training of biomedical and behavioral scientists in areas of national need. They can be in the form of individual postdoctoral fellowships or institutional training grants. After completing NRSA-supported training, recipients are usually expected to engage in biomedical or behavioral research or teaching for a period equal to the period of support.

  — **Individual postdoctoral fellowships.** Individual NRSA's are made to applicants who have received a Ph.D., M.D., or equivalent degree for postdoctoral research training. The award provides the opportunity to carry out supervised research so that biomedical scientists, clinicians, and others can broaden their scientific backgrounds and expand their potential for research in health-related areas. Each applicant must have arranged to work with a sponsor affiliated with an institution having the staff and facilities needed for the proposed training. Federal laboratories, such as those of the NIADDK's intramural programs, as well as universities, medical schools, research hospitals, and similar public or private institutions are among the eligible organizations, and recipients are selected through national competition.

  — **Institutional training grants.** An institutional NRSA may be awarded to a domestic public, nonprofit private, or Federal institution to support a training program in a specific area of research. In most instances, institutions may request support for both pre- and postdoctoral trainees. The applicant institution must have or be able to develop the staff and facilities required for the proposed program and is responsible for selecting trainees. Predoctoral trainees must have received an appropriate baccalaureate degree, and individuals at the postdoctoral level must have received a Ph.D., M.D., D.D.S., D.V.M., or equivalent degree. Institutional grants are for periods of up to 5 years and may be renewed; however, no individual may receive more than 8 years of support (5 years predoctoral, 3 years postdoctoral) unless a waiver is granted by the NIADDK.

  — **Short-term training for students in professional schools.** The NIH has recently initiated a program to provide research experience for talented students in professional schools. The program is designed to help avert a shortage of clinical investigators by attracting highly qualified professional students to careers in biomedical and behavioral research. Domestic schools of medicine, osteopathy, dentistry, veterinary medicine, optometry, pharmacy, and podiatry may apply for grants to support short-term research training for their students for discrete periods of up to 3 months.

  — **Senior postdoctoral fellowship.** Investigators who have held the doctorate for at least 7 years may apply for a senior postdoctoral fellowship. These awards are intended to provide more established investigators with the opportunity to broaden their scientific background and expertise in health-related research. A senior postdoctoral fellowship is usually awarded for 1 year, is subject to NRSA payback requirements, and may not exceed 3 years' total support unless a waiver is granted.

- **CLINICAL INVESTIGATOR AWARD (CIA).** The CIA is directed to clinically trained individuals with demonstrated aptitude in research and provides them the opportunity to develop into independent biomedical investigators. Offering salary support as well as fringe benefits, the CIA program specifically seeks to develop research ability in individuals with clinical background and training. This award is intended to provide research support in the transition between fellowship or trainee experience and a career in independent investigation.

- **RESEARCH CAREER DEVELOPMENT AWARD (RCDA).** The RCDA is a special grant awarded to an institution for support of a named individual. It provides salary and fringe benefits for 5 years, so that the awardee may be relieved of teaching and administrative duties and pursue research interests full time. The program's goal is to provide opportunities for the enhancement of the research capabilities of individuals in the formative stages of their careers who have demonstrated outstanding potential for contributing as independent investigators to health-related research. The awards are available for persons whose research potential is apparent, but who need additional experience in a productive scientific environment.

- **SPECIAL EMPHASIS RESEARCH CAREER AWARD (SERCA).** These awards are sponsored by the NIADDK, in conjunction with other Institutes, for three areas of diabetes research, as follows:

  — Cardiovascular, endocrinologic, and metabolic aspects (with the National Heart, Lung, and Blood Institute).
  — Obstetrical, neonatal, and pediatric aspects (with the National Institute of Child Health and Human Development).
  — Diabetes in the elderly (with the National Institute on Aging).

  The SERCA is intended to encourage qualified individuals who have had clinical subspecialty training but little or no research experience to develop research interests and skills in particular aspects of diabetes mellitus, to provide 5 years of salary support and limited amounts for research expenses to enable individuals to acquire research skills in various basic science disciplines and to pursue a program of research in various fundamental and clinical research disciplines related to diabetes mellitus and its sequelae, and to create a pool of highly qualified investigators with experience and skills in these selected areas of diabetes research for future roles in related areas of research.

- **PHYSICIAN SCIENTIST AWARD (PSA).** The PSA is a new award intended to encourage newly trained clinicians to develop independent research skills and experience in fundamental science and basic biomedical disciplines. It is a 5-year nonrenewable award based on up to five consecutive full-time 12-month appointments. Eligibility is restricted to those holding health professional degrees in the clinical sciences (M.D., D.D.S., D.V.M., D.O. or equivalent). Physicians also holding the Ph.D. are ineligible. Candidates ordinarily will have completed at least 1 postgraduate year of clinical training by the time the award is made. Each candidate must identify a primary sponsor who is recognized as an accomplished investigator in the basic science research area proposed, and who will provide guidance for the awardee's development and research plan. The awardee's program is designed in two phases. In phase I, there is a basic science learning experience that culminates, in phase II, in an intensive research activity under the general guidance of the sponsor. Both individual PSA's and institutional PSA's are provided for.

- **NEW INVESTIGATOR RESEARCH AWARD.** To help bridge the transition from training status to that of established investigator, this award provides funds for relatively inexperienced investigators with meritorious research ideas. The award is designed to encourage the development of research interests and capabilities among both new investigators and those who interrupted their early promising research careers. This special program provides 3 years of nonrenewable research grant support for the initial independent research efforts of new investigators.

as well as graduate, postdoctoral, staff, and faculty positions. Currently, the NIADDK is committed to a level of support of approximately $1.2 million each year.

The Minority Access to Research Careers Program intra-agency agreement with the National Institute of General Medical Sciences enables the NIADDK to increase the number of minority biomedical researchers by making funds available for predoctoral faculty fellowships, visiting scientists, and honors undergraduate training.

Scientists from the NIADDK visit minority institutions, giving scientific lectures and advising students on careers in biomedical sciences. In addition, the Institute's Equal Employment Opportunity Office distributes scientific journals contributed by staff scientists to minority colleges and universities and participates in the Black Colleges Initiative, originated by Executive Order in 1980 to overcome the effects of discriminatory treatment and to strengthen the ability of historically black colleges to provide quality education and participate in federally sponsored programs.

Disease Prevention

In recent years, prompted in part by encouraging developments in the science base, and in part by the increasing cost of health care, the Nation has placed greater emphasis on finding ways to reduce the toll of disease. One way in which the Department of Health and Human Services participates in this goal is through its initiative on disease prevention and health promotion. Modern prevention research has increased in complexity because of the shift in the relative prevalence of such chronic diseases as arthritis and diabetes when compared with acute infectious diseases such as pneumonia and tuberculosis, which were more common at the beginning of the century. The concerns of disease prevention and health promotion among the American people thus have become more challenging to research scientists throughout the country.

The NIADDK has long been involved in prevention-related research, although such activities may not always be labeled as such. The primary product of the Institute is knowledge, the ultimate aim of which is prevention, because prevention of disease clearly is the most useful extension of knowledge in the health field. At the NIADDK, prevention research has as its objectives both the protection of people from disease and the prevention of the progression of disease to disability or early death.

Focus of NIADDK Prevention Research

Many diseases under study at the NIADDK have yielded to basic research, and scientists are now designing means of prevention that will be translated into health-care practice, if they are shown to be safe, effective, and feasible. Many of the projects described in chapters II through V have important implications for disease prevention and health promotion, and major examples of ongoing prevention research activities for each NIADDK Division are highlighted below:

- Prevention of osteoporosis.
- Prevention of complications of diabetes.
- Prevention of obesity and its effects on health.
- Prevention of initial and recurring kidney stones.

Future Prevention Initiatives

In addition to the continuing studies noted above, several other major areas of investigation offer promise for future accomplishments in prevention, for example:

- Research on prevention of injurious consequences of physical exercise and sports activities, such as jogging.
- Research on prevention of the emergence of noninsulin-dependent diabetes mellitus (NIDDM) in genetically predisposed individuals through lifelong weight control and physical fitness (80 to 85 percent of such patients are overweight and physically underactive).
- Research on prevention of recurring peptic ulcers.
- Research on prevention of kidney disease associated with analgesic abuse.
- Research on the factors that predispose older men to the development of benign prostatic hyperplasia, with the aim of eventual prevention or amelioration of this widespread disorder.

Prevention Education and Outreach

Several NIADDK programs that relate to prevention feature interaction with the scientific and public health community, health providers, and consumers. These programs are described in other sections of this report. Major activities are as follows:

- Multipurpose arthritis and diabetes centers.
- Clearinghouses.
- Clinical Nutrition Research Units.

As insight into the causes and development of chronic diseases continues to accrue, new strategies for preventing their onset or destructive progression are being devised. However, it is clear that modification of personal habits and lifestyles—such as

avoidance of obesity and excessive intake of alcohol, dietary changes, and adequate physical exercise—will have an important influence on the degree of success achieved by many of the Institute's prevention initiatives.

Technology Assessment and Transfer

Prior to the scientific revolution of the 1800's, physicians practiced medicine more as an art than a science. With the rapid technologic strides of the last 50 to 75 years, however, the relative advantages of newer methods, devices, and procedures have been identified; innovations have been more readily accepted and adopted; and the discipline of medicine has moved toward the practice of technology-based science.

Determining Research Impact on Health Care

Technology assessment, a form of policy research that examines short- and long-term consequences of the use of technology, is an essential safeguard of the public's right to safe and effective health care. Medical technology assessment is concerned not only with the scientific and medical aspects of advances in diagnosis, treatment, and prevention of disease, but also with indirect, delayed, or unintended social impacts of medical innovation; and, in consideration of economic realities, it vigorously examines and determines the optimal balance among the benefits, risks, and costs of health technologies.

The Office of Program Activities and Evaluation is the focal point for assessing medical technologies conceived, tested, and evaluated in the NIADDK programs and for advising the Public Health Service and other agencies. Technology assessment activities of the NIADDK include workshops, symposia, and consensus conferences to synthesize expert opinion; state-of-the-art reviews of issues within the NIADDK research purview to assist the Public Health Service in the assessment of health technologies; and evaluation of inventions developed in extramural and intramural research.

The NIADDK has participated in approximately 60 national and international scientific conferences, workshops, and seminars in the last year. It also has actively participated in the NIH consensus development program, by which various concerned parties are brought together to seek general agreement on the safety, efficacy, and appropriate conditions for use of a particular medical technology.

During the year, the NIADDK organized, in conjunction with the NIH Office of Medical Applications of Research, a Consensus Development Conference on Liver Transplantation. Experts from throughout the world participated in this effort. Consensus conferences on the prevention of analgesic-associated nephropathy and on the prevention and treatment of osteoporosis are scheduled for 1984.

Utilizing advice from Institute experts and other scientific consultants, the NIADDK provides assessment of medical procedures and treatments for communication to the Health Care Financing Administration, which administers coverage of health services under Medicare and Medicaid. Examples of technologies that have been assessed include:

- Nuclear magnetic resonance (NMR) in diagnosis.
- Thermography (diagnosis by tissue temperature differences, as with breast lesions).
- Portable and wearable artificial kidneys.
- Antigastroesophageal reflux device for prevention of gastric acid reflux and treatment of sliding hiatal hernia.
- Application of catheter irrigation to patients with indwelling urinary catheters.
- Electrocoagulation for the treatment of gastrointestinal hemorrhage.
- Dual photon absorptiometry for bone mineral density determination.

Medical Technology Information Dissemination

The NIADDK recognizes that unless the technologic knowledge gained in basic and clinical research is diffused for application in the health-care community, the value of that research is significantly diminished. Therefore, the Institute devotes significant effort to systems that foster transmission of the latest scientific knowledge and techniques.

The goals of technology transfer are to increase awareness and interest in new research advances, to promote scrutiny and evaluation of their potential advantages, and to foster their trial and adoption in practice. The NIADDK serves a range of constituency groups that includes basic and clinical researchers, health-care practitioners, voluntary and other health agencies, medical educators, and the public. Their individual needs for information are different and may vary at different stages of technologic evolution. Since no single network for information dissemination can satisfy the full spectrum of information needs, the Institute uses varying means to promote the diffusion of information and the transfer of technology:

- *Information collection and dissemination.* The NIADDK's Office of Health Research Reports is the focal point for an integrated program of information collection and dissemination of research highlights, program achievements, and disease-related materials. The office is responsible for coordinating the production and distribution of publications concerning Institute activities; answering inquiries from Congress, the White House, the media, and the general public on the NIADDK activities and disease-related information; providing advice to scientific and program staff engaged in research reporting; and cooperating with voluntary and professional health agencies in the coordination and planning of publications and reports of clinical and research activities.

- *Clearinghouses.* Important components of the Institute's information dissemination program are the Arthritis Information Clearinghouse, the National Diabetes Information Clearinghouse, and the National Digestive Diseases Education and Information Clearinghouse. Their primary objective is to bridge the communication gaps between those who are developing knowledge through research and those who suffer from the effects of these disorders or who direct their care. To this end, the clearinghouses have evolved as national centers for compiling educational materials and information available from various sources, ranging from technical information manuals for health professionals to audiovisual presentations developed especially for elementary school children. In serving as brokers to facilitate the flow of information, the clearinghouses maintain data bases cataloging thousands of brochures, booklets, reports, journal articles, textbooks, and audiovisual materials, and refer clients to appropriate developers or sources, rather than act as distributors of printed matter.

- *Multipurpose arthritis and diabetes centers.* The MAC's and DRTC's have education and demonstration components with information, continuing education, and training programs for medical and allied health professionals and for patients. Of particular importance are programs of education and dissemination of information for the general public concerning new technologies and discouragement of the use of unapproved and ineffective treatment measures.

- *Scientific conferences.* Members of the scientific and medical community, as potential adopters of new technologies, vary widely in their receptiveness to newly communicated innovations. While some investigators and practitioners make particular use of impersonal sources, such as printed materials, to learn about new information, many tend to rely on personal interchange and the experiences of their peer group. Though wider audiences can be reached by journals and textbooks, the information provided by these means is often not sufficiently comprehensive to change attitudes or behavior or to aid in practice. Recognizing that personal communication with associates is an increasingly important factor in information diffusion and technology transfer, the NIADDK continues to support vigorously the conduct of workshops, conferences, and seminars, where representatives of various disciplines can share experiences and discuss different perspectives. The Institute not only provides financial support to such meetings, but sends scientific and program staff representatives to participate in discussions and present reports on the NIADDK research advances.

Program Planning and Analysis

The long-range goal of the Institute is development of applicable knowledge concerning the diseases under its purview, through conduct and support of biomedical research, which would permit their prompt diagnosis, effective treatment, and, preferably, outright prevention. Shorter term objectives encompass the efficient and productive support and conduct of extramural and intramural programs of basic and clinical research related to the individual diseases.

Program planning for research takes place in an atmosphere of uncertainty: conflicting sources of data must be reconciled; knowledge expands; relationships among new findings often are not evident immediately; the timeframe within which new research achievements will occur cannot be predicted; and funding levels often are undetermined. Moreover, decisions regarding research must take into account issues of public health and the public's perception of health needs.

In its planning and analysis activities, the Institute complements its expertise by encouraging broad-based contributions from a variety of individuals and groups: the National Advisory Council and the three national advisory boards, ad hoc scientific advisory groups that counsel the Institute's respective Divisions and programs, other biomedical researchers, and constituent groups. Where societal choices—as opposed to administrative choices—are involved, participation of such outside advisors is especially helpful.

Planning at the NIADDK takes two major forms. The first—strategic planning—involves long-term policy development and comprehensive evaluation of opportunities and problems. For the NIADDK, this type of

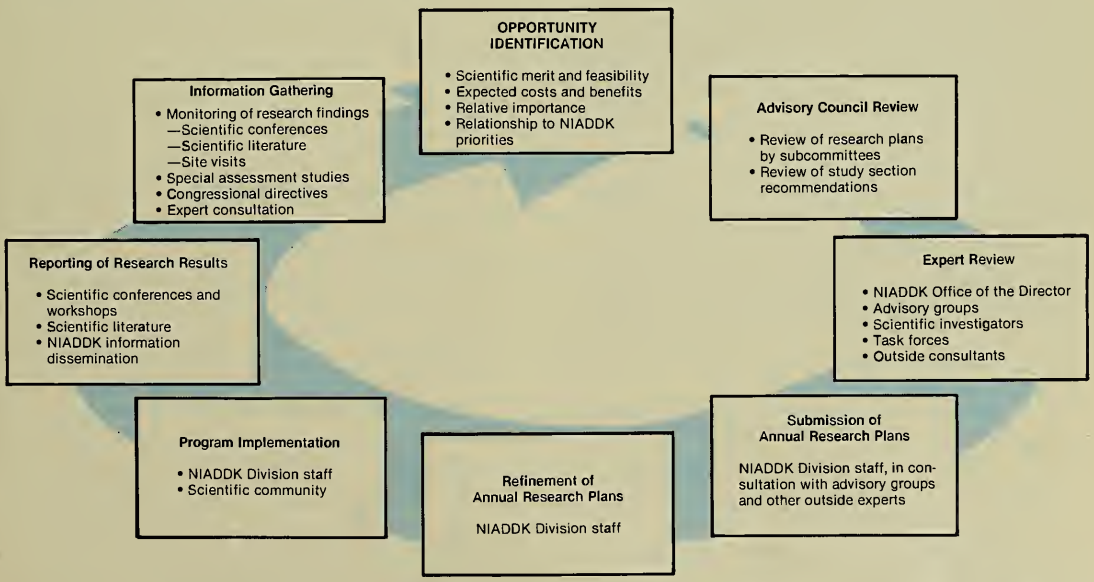
planning was most recently performed, with the assistance of program staff, by the national commissions on arthritis, diabetes, and digestive diseases, as well as by a number of evaluation panels. The other type—implementation planning—is an annual process based on the findings of the more comprehensive strategic planning process; it is dynamic and of more immediate impact, focusing on what the Institute intends for the near future, usually the next 1 to 3 years.

Because the NIADDK relies heavily on investigator-initiated research, new ideas and opportunities explored by the scientific community contribute significantly to the planning process. Also, individual investigators contribute to implementation by developing research grant applications that are pertinent to announced high-priority areas.

To determine its research priorities, the Institute uses a planning process based on a series of steps involving information gathering, progress assessment, opportunity identification, and expert review (see exhibit 8). These steps, which update scientific objectives for use in making decisions on research awards, are as follows:

- Throughout the year, the NIADDK staff regularly monitors the scientific literature, conference proceedings, and progress reports of ongoing research, in addition to visiting the sites of funded research and reviewing investigators' work. Workshops and ad hoc or formal scientific advisory groups are convened in areas of special interest. Congressional directives, plans devised by groups such as the national advisory boards, the advice of professional societies, voluntary health agencies, and consumers, and the results of broad-based evaluation studies organized by the Institute (see below in section on evaluation) are all carefully studied and monitored. These data are then used for assessing progress and identifying scientific advances, opportunities, and Institute initiatives.
- The program staffs of the Institute's four Divisions review such data, and each Division develops, with the assistance of its advisors, an annual research plan. The plans summarize progress, tentatively revise scientific objectives, and delineate specific new activities that show unusual promise. New opportunities and initiatives are ranked by priority on the basis of their scientific feasibility, expected costs, and expected benefits in terms of the advance of scientific knowledge and, ultimately, improved health care.
- The annual plans submitted by the Divisions are then reviewed by experts, including the Office of the Director of the NIADDK, advisory groups, National Advisory Council subcommittees, ad hoc

EXHIBIT 8. Annual NIADDK planning cycle: steps and mechanisms



task forces, and individual scientific experts. For example, elements of the Institute's plan are discussed formally with the Director of the NIH at an annual research-plan review session, at which senior staff members of the Office of the Director, NIH, and of the NIADDK participate. Comments resulting from further expert review are used to refine the plans.

- Once the overall plan has been approved by the Institute Director, it is presented to the Director of the NIH and to the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council.
- The National Advisory Council and its subcommittees participate in Institute planning by reviewing the annual plans of research Divisions, making further refinements. In addition, the four subcommittees and the National Advisory Council as a whole review the recommendations of peer-review groups (the NIH study sections) with regard to the funding of individual research applications.
- Taking the National Advisory Council recommendations into consideration, the NIADDK staff makes awards, giving recognition to the priority scores assigned by the peer review groups, the Institute's financial obligations for ongoing awards made in previous years, and the amount of funds available for new undertakings.

These formal steps in the planning process are designed to ensure that the NIADDK supports new research projects of the highest scientific and technical merit, with full consideration of recent scientific progress, health-care needs, and the availability of funds.

Evaluation of Institute Activities

Evaluation studies provide a rational basis for managerial decisionmaking, for producing statutorily mandated evaluation reports to the Congress and DHHS, and for responding to public concerns for accountability in government. Through such studies, the Institute is able to determine the extent of its progress toward scientific objectives and determine how to strengthen research and administrative activities. Evaluation also provides an effective tool for maintaining balance between programs and mechanisms of funding. The evaluation process is linked closely with long-term strategic planning and contributes to the annual processes of legislative planning and implementation and budget allocation.

The Institute often has commissioned groups of acknowledged experts in one or more of the diverse biomedical disciplines for evaluation of a particular area. Committees are organized to address individual aspects of the general subject, and by the end of the 1- to 2-year study, the group will have examined the state of the art, assessed the contribution of the NIADDK programs, pointed out the most promising directions for future research, and specified particular needs to be met to assure continued research progress. Results of evaluation studies, published as detailed reports and study summaries, have been widely disseminated throughout the scientific community, as well as to Congress and other interested parties.

The Institute also has benefited greatly from the activities of the national commissions on arthritis, diabetes, and digestive diseases, which conducted thorough evaluations of the NIADDK program activities while developing their comprehensive national plans for combating these diseases. Recommendations presented in the commissions' reports have provided a valuable framework for the Institute's strategic planning and policy decisions concerning new initiatives.

The following are some of the NIADDK's recently completed or current evaluation efforts, the results of which are providing impetus for future Institute direction:

- As the NIH lead Institute in endocrinology, and in conjunction with the National Institute of Child Health and Human Development, the NIADDK recently completed an evaluation of endocrinology research supported and conducted by all the NIH Institutes between 1980 and 1983. This was a followup to a previous evaluation (and to its recommendations) of research needs in endocrinology and metabolic diseases conducted for the NIADDK by a group of outside consultants in this field in 1978-79.
- An evaluation of the NIADDK's Hematology Program was conducted to analyze the current state of research in hematology, identify gap areas and the technological advances needed to close them, assess the need for a detailed study of hematology research manpower, and evaluate the extramural hematology program of the NIADDK in relation to the identified needs. Recommendations of the study are being incorporated into the Hematology Program's plans for fiscal year 1983 and beyond.
- A study of the National Diabetes Information Clearinghouse ws undertaken for the purpose of reviewing clearinghouse objectives, activities, performance measures, and performance data. A followup evaluation, using a survey questionnaire, was conducted to assess the utility of materials disseminated by the clearinghouse and the level of user satisfaction. The information obtained from the survey was useful to the program staff in making decisions concerning the discontinuance or addition of certain products and activities.

- The goals, performance, and managerial approaches of the Musculoskeletal Diseases Program have been evaluated to provide a foundation for improving research efforts. This project will also provide an assessment of the health-care impact of selected medical technologies that have been developed with program resources.

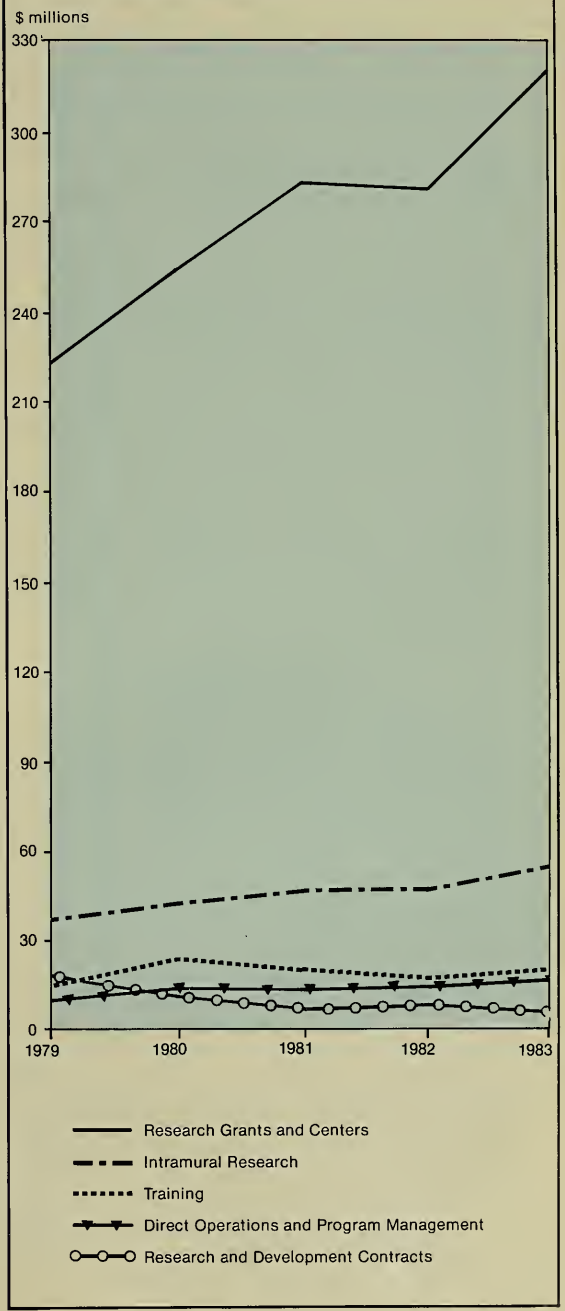
Fiscal Resources

As health research and health care have emerged as major domestic policy issues, the responsibilities of the NIADDK have expanded, and its fiscal obligations likewise have grown. Exhibit 9, which depicts the 11-year change in the five major categories of Institute expenditures, indicates that the annual obligation for research grants and centers had almost tripled by 1981, then settled to a level of $280.8 million for 1982 and has reached $318.4 million (estimated) in 1983. When adjusted for inflation, as shown in exhibit 10, the total annual allocation to the NIADDK has increased by $48.9 million—or 34.2 percent—since 1973.

The NIADDK supports research primarily through the mechanism of investigator-initiated research project grants. There has been a steady increase in emphasis on this mechanism over the years. At the same time, the Institute must maintain a judicious balance among public health needs, the immediate and long-range benefits of planned research, and the research community's need to be self-sustaining, and several types of funding mechanisms must be utilized.

Exhibit 11 demonstrates the relative expenditures for different types of award mechanisms in 1983. Obviously, the greatest portion of the NIADDK's budget is invested in research grants. Applications by extramural investigators seeking grants undergo stringent peer review for scientific merit and compete with other applications in the same area for available current-year funds. The Institute supported 777 new and competing individual research projects in 1983. In large measure, it is this last category of expenditures—the carefully considered allocation of the NIADDK funds among dedicated investigators conducting high-quality basic and clinical research—that has made possible the achievements described in the following chapters.

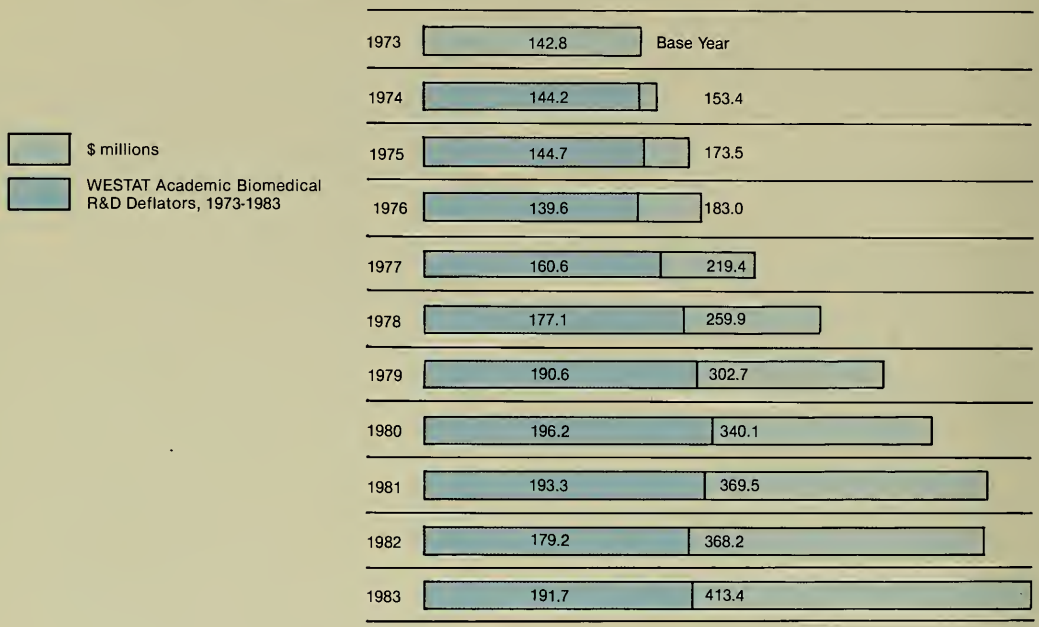
EXHIBIT 9.
NIADDK actual obligations, 1973-1983



Honors and Awards

Many of the outstanding individuals associated with the Institute receive awards or are appointed to organizations and societies reflecting their significant accomplishments. In recognition of outstanding work,

EXHIBIT 10. NIADDK obligations, 1973-1983, adjusted for rate of inflation



grantee scientists around the Nation, intramural scientists at the NIH, Advisory Council and board members, and the NIADDK staff have been honored in the past year. The following is but a sample of individuals who, in the last fiscal year, have received honors or recognition for the work.

Grantees

Dr. Frank Austin, chairman, department of rheumatology/immunology, Brigham and Women's Hospital, Boston, Massachusetts, received the Waterford Biomedical Science Award from the Scripps Clinic and Research Foundation for his contributions to the understanding of chemistry and biology, especially of acute allergic reactions.

Dr. Edmund Y. S. Chao, director of biomechanics and professor of bioengineering at the Mayo Clinic, presented the Shands Lecture at the annual meeting of the American Academy of Orthopaedic Surgeons in March 1983. The following four grantees also received awards at the same meeting:

- Dr. Thomas P. Andriacchi, director of biomechanical research and associate professor in the department of orthopaedic surgery at Rush-Presbyterian-St. Luke's Medical Center in Chicago, received the Kappa Delta Award for his studies on interaction between knee joint mechanics and patient functioning following total knee replacement.

- Dr. Robert H. Fitzgerald, associate professor of orthopaedic surgery at Mayo Medical School, and consultant to the Mayo Clinic, received the Kappa Delta Award for his work on the pharmacokinetics of antibiotics in normal and osteomyelitic bone.

- Dr. William J. Landis, assistant professor of orthopaedic surgery at Harvard Medical School and Children's Hospital Medical Center, received the Kappa Delta Award for his studies of mineralizing tissues.

- Dr. Savio L.-Y. Woo, professor of surgery and bioengineering in the division of orthopaedics and rehabilitation at the University of California in San Diego, received the Elizabeth Lanier Award for his work on internal fixation plates for fracture management.

Dr. Hector F. DeLuca, chairman of the department of biochemistry at the University of Wisconsin, Madison, received the 3M Life Sciences Award ad-

ministered by the Federation of American Societies for Experimental Biology at its annual meeting in Chicago. The award was for his significant contributions to the health and welfare of mankind, including the identification of the metabolically active forms of vitamin D_3.

Dr. Michael Fallon of the University of Pennsylvania received an award as an outstanding young investigator at the June 1983 meeting of the American Society of Bone and Mineral Metabolism.

Dr. Michael Holick, associate professor of nutritional biochemistry at the Massachusetts Institute of Technology, was awarded the Meade Johnson Research Award by the American Institute of Nutrition for his work on the synthesis of vitamin D analogues, including a glucoside that is water soluble.

Dr. Kurt Isselbacher, grantee and former National Advisory Council member, received the Distinguished Achievement Award from the American Gastroenterological Association for his biochemical studies of the structure and function of the gut. Dr. Isselbacher is Mallinckrodt professor of medicine and chief of the gastrointestinal unit, Massachusetts General Hospital, Boston.

Dr. Paul Lacy, former NIADDK National Advisory Council member and professor of medicine at the Washington University Medical School in St. Louis, was elected to the Institute of Medicine of the National Academy of Sciences.

Dr. Daniel McCarty, chairman, department of medicine, Medical College of Wisconsin, gave the Heberden Oration in London, England, in November 1982, at the invitation of the English Rheumatism Society. Dr. McCarty is the fourth American to be so honored (the third was Dr. Lawrence Shulman, NIADDK associate director for arthritis, musculoskeletal, and skin diseases, in 1975).

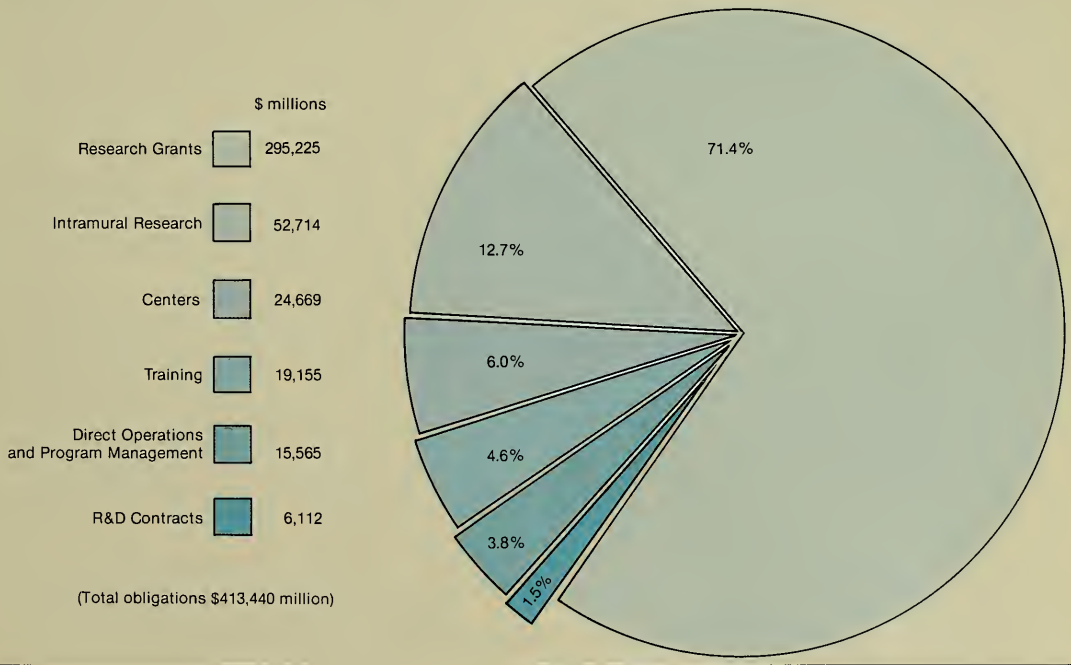
Dr. Van C. Mow, Clark and Crossan professor of engineering at Rensselaer Polytechnic Institute, Troy, New York, and president of the Orthopaedic Research Society, was a recipient of the Melville Medal Award of the American Society of Mechanical Engineers. The award was given for his research on cartilage.

Dr. Hamish Munro, director of the Human Nutrition Research Center on Aging, Tufts University, Medford, Massachusetts, received an award from Bristol-Myers Company for distinguished achievement in nutrition research.

Dr. Lawrence Raisz, head of the division of endocrinology and metabolism, University of Connecticut Medical School, gave the Edwin B. Astwood Lecture at the annual meeting of the Endocrine Society.

Dr. Michael Rosenfeld, professor of medicine at the University of California at San Diego Medical School,

EXHIBIT 11. NIADDK total obligations, by award mechanism, 1983



division of endocrinology, received the Ernst Oppenheimer Memorial Award at the annual meeting of the Endocrine Society in San Antonio.

Dr. Harold Scheraga, professor of biochemistry at Cornell University in Ithaca, New York, was awarded the Linderstrom-Lang Gold Medal of the Carlsberg Laboratory in Copenhagen in recognition of his research in the three dimensional structure of proteins.

Dr. Roger Unger, senior medical investigator and professor of internal medicine at the University of Texas Southwestern Medical School, received the Fred Conrad Koch Award of the Endocrine Society.

Dr. Conrad Wagner, professor of biochemistry at Vanderbilt University, received the Borden Award in Nutrition Research from the American Institute of Nutrition for his extensive work on the transport and metabolism of folic acid.

Dr. Sherman Weissman, professor of molecular biophysics and biochemistry at the Yale University School of Medicine, has been elected to the National Academy of Sciences. His work has been in the area of human genetics, particularly the characterization of repetitive DNA sequences associated with globin genes in thalassemia.

Two grantees were honored by the American Diabetes Association at their annual meeting. Dr. Arthur H. Rubenstein, the former chairman of the National Diabetes Advisory Board, received the Banting Medal for Scientific Achievement for his work with proinsulin and C-peptide (a byproduct of insulin synthesis by the body). Dr. Rubenstein is chairman of the department of medicine, University of Chicago School of Medicine. Dr. Howard S. Tager, director of the Diabetes Research and Training Center and associate professor in the departments of medicine and biochemistry, University of Chicago School of Medicine, received the Eli Lilly Award for Outstanding Scientific Achievement by a Young Investigator.

Advisory Council and Boards

Dr. C. Ronald Kahn, a member of the National Diabetes Advisory Board (and director of research at the Joslin Diabetes Research Center in Boston) was the first recipient of an award from the American Federation for Clinical Research, to be given annually to an outstanding young physician-scientist in the area of clinical research.

Dr. James Klinenberg, chairman of the National Arthritis Advisory Board, has been elected president of the American Rheumatism Association. Dr. Klinenberg is professor and chairman of the department of medicine at the University of California at Los Angeles.

Dr. Eng Tan, member of the National Arthritis Advisory Board (and head of the Autoimmune Disease Center of the Scripps Clinic and Research Foundation in La Jolla, California) was voted Lupus Researcher of the Year by the American Lupus Society.

Dr. Paul Sherlock, chairman of the National Digestive Diseases Advisory Board, received the Distinguished Scientific Achievement Award from the American College of Gastroenterology.

Institute Staff

Dr. Lester B. Salans, director, NIADDK, was elected to the Association of American Physicians in 1983.

Dr. Phillip Gorden, clinical director, NIADDK, was elected to the Association of American Physicians in 1983.

Dr. Gerald D. Aurbach was recently named recipient of one of six 1983 Gairdner Foundation Awards for outstanding contributions to medical science. He is chief of the Metabolic Diseases Branch. Dr. Aurbach was cited for his pioneering work in isolating parathyroid hormone (PTH) and his continuing studies of its mechanism of action.

Dr. David R. Davies, chief of the Section on Molecular Structure of the Laboratory of Molecular Biology, received the Civil Service 1982 Presidential Rank Award of Meritorious Senior Executive.

Dr. Paul A. DiSant'agnese, chief of the Pediatric Metabolism Branch, has received the 1983 NIH Director's Award "For dedicated research and invaluable accomplishments in the field of cystic fibrosis." The Director's Award recognizes exceptional performance by employees who have made substantial or exceptional contributions to the benefit of the programs or the people of the NIH.

Dr. Gary Felsenfeld, acting chief of the Laboratory of Molecular Biology, was given the Public Health Service's Distinguished Service Award (Scientific) for his outstanding research on the structure of chromatin and on the effect of variations in its structure in controlling gene expression.

Dr. Elizabeth Neufeld, chief of the Genetics and Biochemistry Branch, was one of seven NIH-associated scientists to share in the 1982 Lasker Foundation Awards. In addition, she has received the 1983 J. Henry Wilkinson Memorial Award from the International Society for Clinical Enzymology. She was honored for contributions to the understanding of the group of inherited diseases called mucopolysaccharide storage disorders. She also received the Myrtle Wreath Award from Hadassah in April 1983 for her work on genetic diseases.

Dr. Harvey Pollard, chief of the Laboratory of Experimental Pathology and chief of the Cell Biology and Chemistry Section, received the Public Health Science Commendation Medal for his original studies of exocytosis, the mechanism by which neurotransmitters,

hormones, and other cellular products are released from cells.

Dr. J. E. Rall, recently named NIH deputy director for Intramural Research (and former director of the NIADDK Division of Intramural Research), received the Robert E. Williams Distinguished Leadership Award from the Endocrine Society at its annual meeting.

Dr. Kenner Rice, NIADDK research chemist in the Laboratory of Chemistry, received the 1982 Sato Memorial International Award in recognition of his past and present research achievements.

Dr. Jesse Roth, director of the Division of Intramural Research, was selected to receive the Second Annual Otto Brandman Award of the American Diabetes Association-New Jersey Affiliate, in recognition of achievement in the field of diabetes research.

Dr. Phil Skolnick, senior investigator in the Laboratory of Bioorganic Chemistry, received the Mathilde Solowey Award in the Neurosciences. The award was established by the Foundation for Advanced Education in the Sciences at the NIH and honors an outstanding scientist specializing in research in neurobiology or diseases of the central nervous system.

Dr. Howard Smith, medical staff fellow in the Section on Cellular Immunology in the Arthritis and Rheumatism Branch, received the Arthritis Foundation Senior Rheumatology Scholar Award for his research on murine (mouse) lupus at the annual meeting of the American Rheumatism Association. He was also the recipient of the J. D. Lane Junior Investigator Award given by the U.S. Public Health Service for his 1982 research on murine lupus.

Physicians in the Arthritis and Rheumatism Branch have been honored for their collective research efforts in studying systemic lupus erythematosus and especially the nephritis that is a complication of that disease. The branch was awarded the IVth Alessandro Robecchi International Prize at the Xth Congress of the European League Against Rheumatism in June 1983. The award cited the work of branch scientists Drs. John H. Klippel, Howard A. Austin, Paul H. Plotz, Alfred D. Steinberg, James E. Balow (now acting director of the Division of Kidney, Urologic, and Hematologic Diseases for the NIADDK), Margarita E. Kullick, Simon Carette (currently at Centre Hospitalier de L'Universite' Laval, Quebec, Canada), and former branch chief John L. Decker.

Ms. Carol Feld, program analyst in the Office of Program Planning and Analysis, received a cash award in recognition of her outstanding performance as the Institute's coordinator of congressional activities.

Dr. Ernest Johnson, director, Division of Diabetes, Endocrinology, and Metabolic Diseases, received a cash award in recognition of his outstanding management of the Division with emphasis on introduction of valuable innovations and new approaches to the startup of the Diabetes Control and Complications Trial.

Mr. Earl Laurence, executive officer, received a cash award in recognition of his outstanding achievements in administration and dealing with difficult and sensitive management issues.

Dr. Laurence Miller, former program director of (now advisor to) the Skin Diseases Program, was elected to the board of trustees of the Dermatology Foundation.

Dr. Lawrence Shulman, director of the Arthritis, Musculoskeletal, and Skin Diseases Program was honored (along with grantee Dr. Mary Betty Stevens of Johns Hopkins University) by past and present rheumatology fellows of the university at a reception and dinner at the annual meeting of the American Rheumatism Association in San Antonio.

Carolyn Siebert, clinical trials coordinator in the Diabetes Research Programs Branch, was given a Special Recognition Award by the Public Health Service, "for exceptional resourcefulness and initiative as Clinical Trials Coordinator for the NIADDK Diabetes Control and Complications Trial."

Four Institute staff members were recipients of the NIH Merit Award this past year: G. Badman, director, Hematology Program, Division of Kidney, Urologic and Hematologic Diseases, "in recognition of his superior administration of the Hematology Program, NIADDK, and his leadership of the study, Research Needs in Hematology"; Dr. Sarah C. Kalser, director, Liver and Biliary Diseases Program, Division of Digestive Diseases and Nutrition, "for her high level of leadership in directing and administering the Liver Diseases extramural program for the Institute"; Dr. Lois Lipsett, director of the National Diabetes Information Clearinghouse, in recognition of her contribution to the Institute as clearinghouse director; and Dr. Walter S. Stolz, acting director, Division of Extramural Affairs, "in recognition of major contributions to the NIADDK which have exemplified the very highest standards of excellence in health science administration."

The NIH Merit Award is the second highest honor presented by NIH to Civil Service employees. It is designed to "recognize and acknowledge the work of some of the highly motivated and dedicated staff at NIH who have made worthy contributions toward the support of scientific research."

II. Research Focus—Arthritis, Musculoskeletal, and Skin Diseases

Overview

Disorders such as arthritis, diseases of skeletal support structures, and diseases of the skin, while not usually fatal, are among the most common causes of pain, disability, and disfigurement. In addition to the toll they exact in terms of human suffering, the economic impact of these disorders ranges into billions of dollars each year for medical care and lost productivity. Research efforts of the Division of Arthritis, Musculoskeletal, and Skin Diseases, implemented through extramural grant and contract programs, include investigations at major universities and medical schools throughout the country and abroad. Research in these disease areas is also conducted in the NIADDK's Arthritis and Rheumatism Branch at the NIH Clinical Center. Through the NIADDK's efforts over the last three decades, these chronic, crippling disorders have yielded significant ground to research. Depending on the severity or degree of progression, many of these diseases can now be partially controlled with medication and other types of therapy.

More than 31 million Americans suffer from the different forms of arthritis, including some that are fatal.* The economic cost to the Nation is many billions of dollars annually. The term "arthritis" encompasses more than 100 different disorders of the joints and connective tissues, including osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis (spinal arthritis), and gout. Investigation into the area of arthritis was the original mandate of the NIADDK and continues to receive research and programmatic emphasis. While the underlying causes of most types of arthritis remain elusive, considerable progress has been made in some of them. In addition, the NIADDK is actively pursuing basic research into antigens, immune complexes, and aberrations in control of immune processes having a possible relation to arthritis to expand our understanding of those specific viral agents, mechanisms of inflammation, and biochemical abnormalities that have been shown to cause some forms of arthritis and related diseases.

The Division's Musculoskeletal Diseases Program supports studies of properties, growth and metabolism of normal bone, bone and joint diseases, musculoskeletal injury and repair, disorders of skeletal support structures such as tendons and ligaments, and specialized studies in areas such as low back pain and locomotion. The increasingly important areas of exercise pathophysiology and sports medicine are other foci of this program. Research in joint replacement, bone and cartilage transplantation, and fracture healing has helped to restore mobility and freedom from pain for many Americans with orthopedic problems, and preventive approaches promise the eventual control of many of these disorders.

It is estimated that more than 40 million people are affected by these diseases, mainly from bone and joint disorders, fractures, and injuries of the tendons and ligaments.** The resultant economic loss is enormous.

* National Commission on Arthritis and Related Musculoskeletal Diseases.
** American Academy of Orthopaedic Surgeons.

The electron microscope uses beams of high-speed electrons instead of light waves to visualize the organelles and structures within the cell. NIADDK researchers study cells to determine how their functions cause or contribute to disease.

Facing page
Occupational therapist adjusts a handsplint after joint surgery. Improved techniques have expanded dramatically the role of surgery in the management of patients with rheumatic diseases.

Significant advances in measuring bone density by noninvasive methods have enhanced our ability to diagnose and monitor many types of bone disease, such as osteoporosis (reduction in skeletal bone quantity). These improved methods, which obviate the risk and trauma of surgery for biopsy purposes, involve dual photon absorptiometry, computerized tomography, neutron activation, and Compton methods.

The NIADDK's Skin Diseases Program continues to support studies of both normal and diseased skin to obtain a better understanding of cutaneous diseases. The vast group of skin diseases causes a great deal of human suffering through discomfort, disfigurement, or chronic disability. Indeed, skin diseases are a leading cause of industrial disability. The medical, psychosocial, and economic costs of cutaneous disease justify an extensive and diverse research effort.

Skin diseases concern almost all persons in every age group. Many of the skin diseases such as acne, psoriasis, and eczematous and immunologic skin diseases are treatable, in varying degrees, at present; however, the etiology, means of prevention, and cure for most of them are not known. Past efforts have resulted in significant advances in the treatment of selected skin diseases, and there is hope for even greater advancement toward alleviating the damaging effects of such disorders.

Highlights of Research Advances

The following section briefly highlights a number of areas in which the Division of Arthritis, Musculoskeletal, and Skin Diseases has reported recent progress in its research programs.

- In continued studies, rheumatoid arthritis that is refractory to conventional methods of therapy has been shown to respond, for varying lengths of time (up to 4 years), to a sequential irradiation of all major lymph node groups in the body (total lymphoid radiation).
- A recently discovered new form of arthritis known as Lyme disease (after Lyme, Connecticut) has been shown to be caused by a bacterial spirochete carried by a tick. Prompt diagnosis and treatment with antibiotics reduces this type of arthritis and prevents joint damage.
- A marker has been found that predicts which rheumatoid arthritis patients, among those who do not have the characteristic rheumatoid factor in their serum, are at risk for developing severe destructive disease.
- Tests of the drug Tamoxifen (used in the treatment of breast cancer to block estrogen effects) show it can reduce damage to the joints in an experimental osteoarthritis-like condition in laboratory animals. Other methods of osteoarthritis treatment do not alter this disease process.
- Lupus nephritis, the serious and commonly fatal kidney complication of systemic lupus erythematosus, was treated successfully with man-made monoclonal antibodies specific for DNA in the experimental animal model of lupus, New Zealand (NZB/NZW) mice.
- Techniques for knee joint replacement have greatly improved, with good to excellent results in 90 percent of patients on followup.
- A protein recently isolated from human bones, called human skeletal growth factor, has proved to be a potent and specific stimulator of bone cell growth at low concentrations.
- For the first time, an immunologic basis has been found for the localized skin depigmentation of vitiligo; an antibody to pigment cells may be the causative mechanism.
- Circulating antibodies taken from patients with pemphigus, a severe and often fatal blistering disease, can reproduce the human features of pemphigus in experimental animals; such autoantibodies seem to play a causative role in the human disease.
- The mechanism of ultraviolet burns of the skin involves the skin's production of vitamin D_3; intermediates in this process, in turn, facilitate the production of inflammatory prostaglandins.

Arthritis

Spirochetal Etiology of Lyme Disease

Prior Findings

Lyme disease usually begins in summer with a unique skin lesion accompanied by headache, stiff neck, fever, myalgias, arthralgias, malaise, fatigue, or lymphadenopathy. One later symptom is migratory musculoskeletal pain, and still later, frank arthritis may develop. Scientists have found that Lyme disease is associated with characteristic immune abnormalities, and patients with severe disease often have the B-cell alloantigen DR2 (a human leukocyte antigen). The first clue to implicate an infectious cause was the close geographic clustering of affected children in Lyme, Connecticut. The disease is now known to occur in at least 14 states, in Europe, and in Australia.

Subsequent investigations indicated that the disease was carried by a newly identified tick. Next, researchers discovered that early antibiotic treatment could shorten disease duration and lessen or prevent the severity of subsequent arthritis. This finding

suggested that the cause was a penicillin-sensitive bacterium such as a spirochete.

Recent Advances

In 1982, a previously unrecognized spirochete was isolated from ticks (*Ixodes dammini*) in an area known to be endemic for Lyme disease. Nine patients with Lyme disease were shown to have high antibody levels against this organism. Recently researchers have isolated the same spirochete from the blood, skin lesions, or cerebrospinal fluid of 3 of 56 patients with Lyme disease, as well as from the tick associated with the disease. All three patients were quite ill at the time of culture. The difficulty in recovering and culturing the organism suggested that the number of organisms in affected tissues is generally small. However, in selected Connecticut geographic areas, researchers have found spirochetes in 20 percent of nymphal and adult ticks. The spirochetes were found in 60 percent of the ticks on Shelter Island, New York, where numerous Lyme disease cases have occurred. These prevalences of infected ticks are high, but consistent with the large number and close geographic clustering of reported cases of Lyme disease. The culture of the *Ixodes dammini* spirochete now permits definitive but low-yield diagnosis. More importantly the isolation of the disease agent and its immunologic characterization are important steps toward treatment and prevention. Specific patterns of antibody formation accompany the disease in its early stage of skin lesions (elevated immune globulin M) and in its later stage of nervous system, heart, or joint involvement (elevated immune globulin G).

Research Directions

Scientists are currently testing antibiotic sensitivities against spirochetes. It is hoped that tests of the efficacy of high-dose penicillin in other spirochetal infections, such as meningoencephalitis, will also be relevant.

The later manifestations of Lyme disease may mimic other immune-mediated disorders, including juvenile rheumatoid and other rheumatoid arthritis, Reiter's syndrome, and rheumatic fever. Unlike other spirochetal infections, the late manifestations of Lyme disease consist primarily of arthritis. As yet it is not known whether the spirochete is still present at that time or whether it simply initiates a self-propagating inflammatory response. The question of whether immune-mediated diseases require a persistent infectious agent or whether such an agent triggers disease followed by autoimmunity is of central importance.

Immunogenetic Markers and Rheumatoid Arthritis

Prior Findings

Serum rheumatoid factor (RF) and DR antigens (inherited tissue-type antigens) are well-known to be associated with rheumatoid arthritis. However, 10 to 30 percent of persons with rheumatoid arthritis do not show a detectable level of serum RF. In addition these seronegative patients have been observed to have milder disease. While certain histocompatibility DR antigens (HLA DR4) also are known to be associated with seropositive arthritis, findings concerning the association of DR antigens and seronegative RF have been limited and contradictory. Until recently, it was not known whether seronegative and seropositive rheumatoid arthritis were the same or different disorders, and it was not known whether DR antigens had any relationship to disease severity in seronegative rheumatoid arthritis.

Recent Advances

NIADDK grantees have recently examined the relationship between seropositive and seronegative rheumatoid arthritis, to determine whether or not the disorders are distinct diseases and how DR antigens relate to disease severity in both seropositive and seronegative rheumatoid arthritis. In this study, 140 randomly selected patients with rheumatoid arthritis were examined. Complete HLA (DR antigen) typing for 110 patients was obtained, and strict criteria were used to identify 80 seropositive and 30 seronegative patients. The patients were categorized carefully to determine the severity of their disease, and these data were compared to data concerning serum RF and DR antigens.

Although seropositive patients showed an increase in DR4 (and a decrease in DR3 and DR7) antigens, there was no correlation between different DR antigens and disease severity in the seropositive patients.

In sharp contrast, seronegative patients showed a correlation between DR4 and more severe disease. Thus, it appears that seronegative and seropositive rheumatoid arthritis are immunogenetically distinct disorders. Moreover, data suggest that DR4 is a newly known marker for disease severity in seronegative patients. Seronegative patients who are DR4 positive should be considered a high-risk group for developing destructive disease.

Research Directions

Only small numbers of patients with DR4 positive seronegative characteristics have been examined, and comparable studies of additional patients will be needed to determine the influence of DR4 and the clinical manifestations of seronegative rheumatoid arthritis. Moreover, the fact that seronegative and seropositive rheumatoid arthritis appear to be immunogenetically distinct disorders will require investigation to determine other possible differences between the two disorders and the possible implications of differing modes of treatment.

Arthritis Treatment With Total Lymphoid Irradiation

Prior Findings

Total lymphoid irradiation (TLI) is a technique of radiation (X-ray) of each of the body's lymph node groups in sequence, originally developed to treat stage III Hodgkin's disease. Recently the technique has been suggested as a possible therapy for patients with intractable rheumatoid arthritis as well as other autoimmune diseases and organ transplantation. In a 1981 report, TLI was suggested as an efficacious treatment for patients with very far advanced and crippling autoimmune disease. In early reports from a study of 11 cases of rheumatoid arthritis, 9 patients showed clinical improvement. Continued monitoring of these rheumatoid arthritis patients has shown continued improvement over a period of 4 years. Although intermittent flareups of joint disease did occur in some patients during the first few months of study, about 1 month after the full course of TLI, 9 of the 11 patients showed significant reductions in morning stiffness, joint tenderness, joint swelling, and improvement in overall function scores. No patients experienced major side effects.

In addition, the responding patients' lymphocyte count dropped drastically, from 1,621/mm^3 to less than 200/mm^3, and stabilized at a mean of 668/mm^3. The mean absolute number of T cells fell to about one-third of the pretreatment number, and a marked change occurred in the ratio of T lymphocytes that suppress the production of antibodies to those that help in their production. Prior to irradiation the ratio was 0.45. After TLI, the ratio was 1.32 and remained at that level. These encouraging results have stimulated development of a large-scale clinical trial.

Recent Advances

Two years or more after the 11 patients receiving TLI had completed the treatment, the 9 who had had a remission (relief of symptoms and signs of disease) were still in remission.

A team of investigators is now three-quarters of the way through a prospective randomized clinical trial of TLI involving a larger number of rheumatoid arthritis patients. Results are expected to be reported late in the summer of 1983. If the results reflect earlier successes, we will be able to say with some conviction that TLI is an efficacious and apparently well-tolerated, low-morbidity treatment for patients with advanced rheumatoid arthritis.

Research Directions

Researchers are currently investigating optimal radiation dosages and variations in irradiation techniques. In addition, investigations of TLI therapy in patients with systemic lupus erythematosus and in patients needing kidney transplantation are also under way.

TLI therapy has no effect on levels of rheumatoid factors, antinuclear antibodies, and immune complexes. Research is needed on the significance of this finding for understanding the basis for TLI's action and whether TLI remissions actually change the natural course of the disease process.

Utilization of Radioisotopes for Destruction of Diseased Joint Tissue in Patients With Rheumatoid Arthritis

Prior Findings

The major cause of pain in rheumatoid arthritis is the inflammatory response in the synovial lining of affected joints. Continued inflammation not only perpetuates pain, but ultimately destroys articular cartilage. The central role of the inflamed synovium in joint destruction suggests that early control of the inflammatory process or ablation of the inflamed synovium, through its surgical removal (synovectomy), would either prevent or delay joint destruction; but, recurrence rates are high, and the procedure involves significant discomfort.

Recent Advances

An alternative to surgical synovectomy is the use of radioisotopes, by intra-articular administration, to destroy the diseased synovium. An animal model of immune arthritis has been used to evaluate various radiopharmaceuticals, and methods of packaging these isotopes to avoid systemic spills, to produce an effective synovectomy.

Of five potentially useful radioisotopes, the use of 165 dysprosium attached to a ferric hydroxide microaggregate has been found to be the most promising. The appropriate dose that will produce synovectomy without damaging articular chondrocytes has been determined.

Animal studies have been extended to humans with symmetrical rheumatoid involvement of the knees. The effectiveness of the resulting synovectomy has been evaluated by both clinical observations and objective scanning. Improvement in articular function and objective parameters in 80 percent of patients treated for periods of 12 months has been reported.

Research Directions

The period of observation of these studies must be extended for several additional years to ascertain that these positive findings are not temporary. Also, clinical studies with dysprosium and additional research toward production of new isotopes and new particle

systems, to extend and improve these preliminary results, should continue.

Experimental Model for Studying Proliferative and Destructive Lesions of Rheumatoid Arthritis

Prior Findings

Rheumatoid arthritis results primarily in destruction of articular and periarticular structures. Symptoms range from joint pain and stiffness to disabling deformities. In rheumatoid arthritis, the synovial membrane typically becomes thickened due to cell proliferation and an influx of immune cells. The synovial cells have been found to produce both collagenase and prostaglandin E_2, which may contribute to the destructive lesions. Because of the cells' destructive capacity, it is important to study the role of both collagenase and prostaglandin E_2 in the inflammatory process. However, the synovial cells are difficult to study in culture.

Recent Advances

Researchers have recently used the immunologically weak "nude" mouse as a host in which to implant synovial tissue to study morphology, survival, and production of collagenase and prostaglandin E_2 (PGE_2) by synovial cells. They have found that injected cells remained at injection sites for at least 3 weeks, during which time they organize into a structure closely resembling the rheumatoid synovium. The cells were found more able to synthesize and secrete collagenase and PGE_2 than cells grown *in vitro*. Thus, the nude mouse provides a better environment for studying the biology of rheumatoid cells than does tissue culture.

Research Directions

Changing the conditions under which synovial cells grow in the nude mouse may yield further information about how these cells grow in humans. As an example, nude mice that have been injected with synovial cells can be treated with various drugs to investigate the various physiological capabilities of the cells and as a way to alter the course of the disease process.

Monoclonal Antibodies to DNA Shown to Reduce Mortality From Lupus Nephritis in Animals

Prior Findings

Systemic lupus erythematosus (SLE) is a chronic inflammatory connective tissue disorder that occurs primarily in young women. Its cause is unknown. Its symptoms are varied and may include fever, cutaneous lesions, arthritis, pleurisy, and kidney problems (lupus nephritis) that can result in death. Treatment ranges from salicylates and chloroquine to stronger drugs such as corticosteroids and other immunosuppressive drugs. Treatment may be difficult in severe cases and can involve lifelong maintenance with steroids. While often effective, this course of treatment can have harmful side effects.

Recent Advances

Investigators have recently developed monoclonal antibodies that are specific for double-stranded DNA. These antibodies have been injected into various inbred mouse strains, which provide an experimental model of spontaneous SLE and immune nephritis. Without treatment, such animals usually succumb to immune nephritis within 6 to 8 months. When 6-week-old mice were injected with these monoclonal antibodies, all were found to be alive at 7 months of age, in contrast to a 60 percent mortality rate found in untreated mice. When tested at 7 months of age, the serum of the treated group of mice was found to have a greatly reduced quantity of antibodies to double-stranded DNA. This new approach to therapy may have great potential in treating SLE in humans.

Research Directions

It is now important to determine the mechanism by which this increased survival occurs. Some possibilities include activation of a population of suppressor T cells or destruction of B cells that produce antibody to anti-DNA molecules.

Interferon Levels in SLE Patients

Prior Findings

In both SLE and other rheumatic disorders, patients display elevated levels of circulating interferon (IFN). The substance has been of special interest in the autoimmune diseases because it has been shown that high doses of IFN suppress antibody formation, but low doses enhance antibody production. Thus, it has been hypothesized that IFN plays a significant role in regulating immune responses to viral, pharmacologic, and bacterial insults. Over several years of study, scientists have identified at least three different types of IFN. Type I IFN is a glycoprotein produced by cells in response to viral infection or exposure to a variety of drugs and bacterial polysaccharides. Type II IFN is closely related and is produced by lymphocytes stimulated by nonspecific mitogens. Type I IFN has now been subclassified into two substances, one produced by leukocytes and the other by fibroblasts. Until

recently, it was unknown whether one or all three of the IFN types play a role in rheumatic disease activity.

Recent Advances

Recently investigators have found a relationship between types of IFN and several parameters of SLE disease activity; IFN levels were found to correlate with both clinical disease activity and anti-DNA binding, but not with serum complement levels. Seventy-seven percent of serum samples taken during SLE disease activity contained measurable amounts of IFN. Similar results were obtained regarding anti-DNA antibody levels. The IFN type produced by leukocytes was the type found in SLE sera.

Research Directions

Because of the many documented immunomodulating effects of IFN, the possibility that IFN itself might be responsible for the immune aberrations in SLE should be considered. It is also possible that IFN may function as a mediator of clinical disease expression in SLE.

Investigators have observed in mice that IFN can increase autoimmune disease activity, and investigations should be made of the possible pathogenetic role IFN may play in mediating the autoimmune diseases.

Testosterone Oxidation in Systemic Lupus Erythematosus

Prior Findings

Sex steroid metabolism is of considerable interest in the study of SLE because of the large numbers of women with SLE and the recently described abnormal estrogen metabolism in both men and women with the disease. In addition, there have been reported beneficial and adverse effects of sex hormones on experimental models of SLE.

Recent Advances

Recently, androgen metabolism also has been studied, particularly the oxidation of testosterone at the C-17 position, in volunteers and patients with SLE. The total extent of oxidation of this male hormone was found to be elevated in women with SLE when compared with normal women. In contrast, males with SLE did not differ from normal volunteers. Age, severity of disease, and steroid therapy did not appear to have any effect on the extent of oxidation. Thus, women with SLE have a distinct abnormality in androgen metabolism. This is of interest because the products of C-17 oxidation of androgens can potentially become estrogens.

Research Directions

Further studies are necessary on the clinical significance of abnormal metabolism of androgens in women with SLE and on the implications of this finding for treatment of patients with the disease.

Tamoxifen Treatment for Osteoarthritis

Prior Findings

Osteoarthritis is a degenerative joint disease that afflicts 16 million Americans, most of whom are over 50 years old. Clinicians have noted that the symptoms of osteoarthritis become worse in postmenopausal women, and it is suspected that sex hormones play a role in cartilage metabolism and development of the disease. In the past, various hormones have been tested but none has been found to be of value in treatment. Moreover, drugs commonly used to treat arthritis, such as aspirin, corticosteroids, and chloroquine, have not altered the disease process. Because it had been observed that estrogen increases joint damage, it was suggested that perhaps an estrogen-blocking drug would have a beneficial effect.

Recent Advances

Tamoxifen, an estrogen-blocking drug used in treating breast cancer, recently has been studied for its effects on osteoarthritis. Investigators used a well-established animal model, the New Zealand white rabbit. Three groups of 17 rabbits were studied. One group received a placebo, one, a potent estrogen (estradiol), and the third group was given Tamoxifen in doses that approximated those used for breast cancer. The control group and that receiving estrogen showed no improvement; however, the group receiving Tamoxifen showed significantly reduced frequency of joint damage. The researchers point out that Tamoxifen did not reduce the incidence of osteophytes—bony outgrowths that they and other scientists believe may be caused by instability of the joint rather than by the erosive osteoarthritic process.

Research Directions

It is not yet known whether Tamoxifen's beneficial effect is due to its antiestrogenic effect or some other mechanism. Studies are planned to determine Tamoxifen's method of action and to assess its ability to retard the disease process and perhaps repair already established osteoarthritic damage.

Loading Inhibits Recovery From Induced Atrophy in Dog Knee Cartilage

Prior Findings

It has been shown that the atrophy of knee cartilage that develops when the hind limb of a normal adult dog is immobilized in a cast for 6 weeks is accompanied by decreases in uronic acid content and net prostaglandin synthesis. Furthermore, newly synthesized prostaglandin from cartilage of the immobilized limb does not aggregate in culture, due to an apparent abnormality in the hyaluronic acid-binding region of the prostaglandin core protein. All of these effects of immobilization are rapidly reversible, if the casts are removed and the dogs are allowed to walk on all fours for 3 weeks. These findings suggest that exercise is necessary for repair processes to function. However, it is not known what kind and degree of exercise have the most beneficial impact.

Recent Advances

A recent study has extended previous observations by examining the effect of immobilization on total tissue proteoglycans to answer the important question: Do chondrocyte injury and articular cartilage damage result if a limb is vigorously exercised immediately following a period of immobility—at a stage when the cartilage is atrophic and the macromolecular organization of the matrix is defective?

The effect of vigorous exercise on the reversibility of canine knee cartilage atrophy was examined. In comparison to cartilage from normal knees, cartilage from immobilized knees showed an increase in water content and decreases in thickness, safranine O staining of the matrix, uronic acid content, and net proteoglycan synthesis. In addition, the ability of both newly synthesized (35S) and total tissue proteoglycans to interact with hyaluronic acid to form aggregates was diminished. If the casts were removed and the animals were then allowed to walk freely for 3 weeks, all of these changes were reversed. However, knee cartilage from three dogs that had been run daily on a treadmill showed continuing abnormalities even though net proteoglycan synthesis was increased. Furthermore, the abnormality in both 35S and total tissue proteoglycans persisted. In this respect, the proteoglycans were indistinguishable from those obtained from knee cartilage immediately following 6 weeks in a cast.

The results show that when the integrity of the extracellular matrix of articular cartilage has been diminished by immobilization, it may be vulnerable to loading during subsequent exercise and that may damage the chondrocyte and affect its capacity for repair.

Research Directions

More studies are needed to establish the relationship among atrophy, exercise, and exercise loads in experimental conditions as well as in osteoarthritis in humans.

The Association of Amyloid Deposits and Osteoarthritis

Prior Findings

Amyloid (an abnormal glycoprotein usually associated with long-term immune or inflammatory diseases) in and around joints has been regarded as a rare occurrence. Local deposits of amyloid have been identified in the fibrous capsule of the hip and the fibrocartilaginous disk of the sternoclavicular joints, in elderly patients with osteoarthritis.

Recent Advances

Recently, amyloid deposits have been found in association with calcium deposits (in joints of patients with pseudogout). To confirm the presence of localized amyloid in articular structures, previous closed synovial membrane biopsy specimens in rheumatoid arthritis and osteoarthritis were examined. Amyloid deposits were found in a surprising proportion of synovial membranes from patients who had osteoarthritis, although the initial expectation was to find them in rheumatoid synovia.

A further prospective evaluation of patients with osteoarthritis, examining synovium, articular cartilage, and cartilage removed during arthroplastic surgery, revealed that more than half the patients studied had age-related amyloidosis. Present results and previous reports have found a correlation of amyloid deposits with the duration and severity of osteoarthritis.

Research Directions

Whether the amyloid associated with osteoarthritis is an incidental finding or of pathophysiological importance is not yet known, but should be subject to further study.

Epidemiologic Studies Examine Genetic and Environmental Factors in Rheumatic Diseases

Prior Findings

Rheumatoid arthritis occurs worldwide and has been studied in diverse populations. Many epidemiologic studies have reported a fairly constant prevalence of 0.5 to 2.0 percent. Populations that differ significantly

from this range might provide a means to study special factors related to disease etiology.

Recent Advances

Investigators have been studying the prevalence of inflammatory joint diseases in two highly inbred populations, the Mille Lacs Band of Chippewa Indians and the Old Order Amish. An unusually high level of rheumatoid arthritis (a prevalence of almost 7 percent) has been found in the Chippewa Indians. In the Amish, researchers have discovered that two other rheumatic diseases, sacroiliitis and ankylosing spondylitis, are present in large numbers. These two forms of spinal arthritis have also been found to be associated with the major histocompatibility antigen (inherited tissue type), HLA-B27. Detailed studies of 57 Amish couples have confirmed a high prevalence of sacroiliitis in this inbred population, but this is not associated with HLA-B27, and other causative factors should be sought.

Research Directions

Both of these populations need to be examined in greater detail, including more extensive histocompatibility antigen testing, detailed family studies, and search for common environmental factors, to determine what the relative contributions of the environment and the genetic background to disease development are.

Musculoskeletal Diseases

Growth Factors Mediating Bone Cell Differentiation

Prior Findings

Both in humans and animals, bone is constantly changing. Old or damaged bone is dissolved, and new bone is synthesized to replace it. In healthy adults, these processes are in balance, but in some disorders, the dissolving (resorption) processes dominate, and bones become less dense and more fragile. Scientists have hypothesized that the process of bone resorption and replacement is mediated by a chemical released during resorption, and the agent may then stimulate synthesis of new bone. A protein called human skeletal growth factor (hSGF) has been postulated to be the coupling agent that regulates this process.

Recent Advances

For the first time, hSGF has been isolated from human bones and has been shown to stimulate their growth. The growth factor was isolated from human femoral (thigh bone) heads obtained during hip replacement surgery. The protein is a potent growth factor for bone cells at low concentrations. A level of 0.3 microgram per millimeter increases DNA synthesis in a standard cell proliferation assay, more than doubling DNA synthesis as compared to control cells. The same concentration increases the growth rate of cultured embryonic chick leg bones (tibiae and femora) to 164 to 185 percent of controls. In cultured human bone cells, it increases the growth rate to 1,090 percent of controls. It has little effect on other types of cells. In addition, several related proteins also have been isolated in both animal and human cells, but it is not known whether these growth factors are specific for certain cells, such as cartilage, or for certain developmental patterns of fetal skeletal growth. In related findings, scientists have isolated other proteins that appear to initiate differentiation of primordial cells into bone cells and have found still other proteins that may be used to repair bone defects in humans.

Research Directions

Scientists are now working to produce antibodies to hSGF; however, bone proteins are usually weak antigens, and production of their antibodies is difficult. Attempts are being made to modify the hSGF protein to be tested in blood. An antibody to the hSGF is of special interest in Paget's disease, which is a chronic disorder characterized by localized enlargement and deformity of the skull, spine, and long bones due to unregulated, abnormal bone-cell multiplication.

A clearer understanding of bone factors controlling bone metabolism is a major issue in normal bone physiology. Controlling or replacing specific factors may be therapeutic for many bone disorders. Bone healing and repair may be improved. Attachment of joint replacements could be enhanced with such bone growth inducers.

Work should be pursued to identify and purify the most active proteins (or their subunits). Because of the cyclic nature of the bone remodeling process and the many agents affecting the process, complete understanding of these factors will require extensive and lengthy exploration and evaluation.

A highly informative workshop on this topic, cosponsored by the NIADDK and the National Institute of Dental Research, was held in May 1983.

Mineralization of the Growth Plate

Prior Findings

Many factors have been identified as influencing the complex process of bone formation in cartilage. One theory describes the breakdown of large proteins (proteoglycans) into fragments that are removed before calcification could occur.

Recent Advances

Recent immunofluorescent localization studies of proteoglycan components (monomer and link protein) in growth plate show that these substances do not diminish in response to calcification. These chemical investigations, along with electron-microscopic studies, suggest a displacement of monomers within the proteoglycan aggregate. Autoradiographic and biochemical studies have demonstrated that phosphoproteins are present in the highest concentration in the mineralization region. A new protein has been isolated that is selectively concentrated in the region where mineralization begins. Both of these new results suggest that specific proteins control the mineralization process.

Research Directions

Longitudinal growth of bones is a major event in the maturation of the skeleton. Studies on this subject also relate to the continuous remodeling that bone will experience after its original formation.

Extension and further validation of these osseous studies should be the initial aim of this research. Eventually the development of clinical therapies for growth defects may emerge.

New Techniques Permit Knee Joint Replacement

Prior Findings

Hip joint replacement has become a widely used, successful procedure to relieve pain and dysfunction in many patients. The recent NIADDK-sponsored Consensus Development Conference on Total Hip Joint Replacement noted a 90 percent success rate 10 years after implantation. Until recently, however, replacements of other body joints with man-made prostheses have not had such positive outcomes.

Recent Advances

Knee joint replacement technology has evolved from a fixed-pin axis device to a semiconstrained prosthetic arrangement. Current designs permit only a small portion of the rotational torque (stress) to be transmitted through the joint. In a recent 3- to 5-year followup of 183 patients using the Hospital for Special Surgery scoring system, 90 percent of the patients with these devices had good to excellent results. The reoperation rate was found to be less than 4 percent. Preliminary, but encouraging, data also suggest success with other joints, such as the elbow, using this partially constrained design concept.

Research Directions

Several investigators are developing mathematical models and experimental gait laboratories to study prosthetic performance. This information should be used to evaluate quantitatively the pre- and postoperative performance of subjects with various replacement devices. Using these techniques, it may be possible to detect and quantitatively determine subtle differences among the various joint replacement component designs.

New Information on the Basic Mechanisms of Low Back Pain

Prior Findings

Low back pain and its resulting disability have a major socioeconomic impact. The normal and diseased components of the spine are being studied to gain an understanding of this complex disorder. A common cause of low back pain is herniation or rupture of an intervertebral disk, specifically its center, the nucleus pulposus. This disk of cartilage may be extruded from between two vertebrae and cause pressure on nerve tissue (as occurs with sciatica due to lumbosacral disk herniation). Although the defect commonly follows an injury (and may do so many years later), little is known about risk factors and actual causative mechanisms. Research on the connective tissue making up the nucleus pulposus and the surrounding ring of fibrous strands (annulus) that restrain it is providing some of the necessary information for understanding and preventing this source of low back pain.

Recent Advances

The major protein of the nucleus pulposus is type II collagen (classified as type II on the basis of its molecular composition). The type II collagen of the nucleus pulposus is more extensively cross-linked (one fiber to another) than any other skeletal collagen. The (type I) collagen of the restraining annulus is less densely cross-linked. Disk samples from one group of back pain sufferers showed a severe decrease in density of mature collagen cross-links. Thus, the level of cross-linking in an individual may be a risk factor for degenerative disorders of the skeleton.

Other NIADDK grantees have examined the ground substance in which the collagen fibrils are embedded. The ground substance is made up of proteoglycan, a complex of protein and carbohydrate derivatives (glycosaminoglycans). These glycosaminoglycans have demonstrated a spectrum of forms of proteoglycan in the nucleus pulposus, based on the size and nature of the aggregates of this material. A high proportion of the molecules present in the semiliquid nucleus

pulposus are breakdown products of the large aggregates. A balance between synthesis, breakdown, and removal must exist to allow the nucleus to maintain its functional role.

A new study has begun to evaluate the enzymatic dissolution of the nucleus pulposus using chymopapain (an enzyme that can digest and dissolve ground substance in cartilage). Preliminary findings show that the cartilage cells remain viable, and disk material can be reconstituted into cartilage. This experimental finding has potential importance for the understanding and treatment of herniated disks.

Research Directions

The significance of the density of collagen cross-linking as a predictor for future back disorders needs to be defined; such a predictor would allow early preventive measures to minimize or avoid skeletal damage in individuals at risk. Further work on the ground substance of the cartilage in the nucleus pulposus should be pursued to identify the necessary conditions for its functional integrity and the reasons for its failure. Studies on the reconstitution of cartilage after chymopapain dissolution should be pursued for their possible future applications.

Effect of Exercise on Muscle Tissue

Prior Findings

With intense national interest in exercise and physical fitness, new effort has been directed toward understanding how muscle responds to exercise and weight training. Muscles enlarge as the result of weight lifting, and one theory is that this enlargement occurs because the muscle fiber splits, resulting in an increase in the number of fibers. Recent evidence, however, shows that the number of muscle fibers is relatively constant and is established early in skeletal maturity. Thus, new theories must be developed to explain how muscles enlarge with exercise.

Recent Advances

Muscle performance characteristics are determined by the oxidative status (low or high) and the twitch speed (fast or slow) of a particular muscle. In general, regular exercise delays fatigue and sustains the muscular supply of ATP (adenosine triphosphate, a chemical mediator of energy). Muscle fatigue and recovery is different in the separate types of muscles. For example, slow soleus muscle (in the lower leg) recovers from fatigue in less than 1 minute; fast muscles require approximately 1 hour. In one experiment, overloaded fast muscles were shown to convert to slow fibers. This suggests that interactions of these two types of fibers may play a role in muscle building and in decreased fatigability subsequent to regular exercise.

Research Directions

The precise relationship of fast and slow muscle fibers is unknown. Further studies are needed to elucidate conversion processes, the effects of various exercise regimens, and other exercise-related phenomena. Studies should be continued with various exercise states, using advanced biochemical and ultrastructural technology. Higher species animal models may be required in some future work. Recently, histologic and immunocytochemical technology was developed to identify subtypes of fibers. This area may open new dimensions in understanding muscle physiology.

Skin Diseases

Blistering Disease Studied With Monoclonal Antibodies

Prior Findings

Widely used techniques that employ special cells for the production of highly specific (monoclonal) antibodies have now been adapted to the study of normal and abnormal skin components. Monoclonal antibodies can be raised that are specific for many different biologic macromolecules. These techniques have been utilized in various studies of the macromolecules of skin, both in epidermis and dermis, and in the basement membrane zone that connects the two.

Recent Advances

Institute grantees have prepared monoclonal antibodies against human epidermal keratins and have used them to study keratin expression during normal epidermal differentiation. Workers at NIH using monoclonal antibody and other techniques have demonstrated the presence of a protein called laminen in the basement membrane zone and have shown that its size, shape, and binding sites indicate that it may be important in binding the basal cells of the epidermis to the collagen of the dermis.

Applying these techniques to the hereditary, often fatal blistering disease(s) epidermolysis bullosa, other grantees have demonstrated that a monoclonal antibody to human fibrils anchoring the epidermis reacts with these structures in the underlying (papillary) dermis of normal individuals, but that there is no demonstrable binding in the papillary dermis of nonblistered skin of patients with the dystrophic form of epidermolysis bullosa. Independently, investigators at NIH have isolated a monoclonal antibody that binds to a noncollagenous constituent of a layer (the lamina densa) of the basement membrane and have demonstrated that binding of this antibody is absent or faint in recessive (derived from only one parent) dystrophic

epidermolysis bullosa and reduced in dominant (derived from both parents) dystrophic epidermolysis bullosa. Binding was normal in epidermolysis bullosa simplex (a dominant form without later scarring, in contrast to the dystrophic form), parents of recessive dystrophic epidermolysis bullosa, and normals. They have also demonstrated binding of this antibody to normal fetal skin at 25 weeks' but not at 14 weeks' gestation. Thus, these studies demonstrate a possible pathogenic mechanism for some important forms of epidermolysis bullosa and the basis for possible prenatal diagnosis.

Research Directions

Work is needed on the application of these findings to prenatal diagnosis of epidermolysis bullosa. If successful, the technique would be valuable in counseling prospective parents. Other applications to the study of skin should be explored.

Demonstration of the Pathogenicity of Autoantibodies in Pemphigus Vulgaris

Prior Findings

Pemphigus vulgaris is a severe and often fatal disease that affects the skin and mucous membranes and in which intraepithelial blisters form. Almost 20 years ago, antibodies were found to be a marker of this disease; however, in the ensuing time period, conclusive proof that these autoantibodies actually cause the disease has not been found. The lack of this evidence has impeded research into the basic cause of the disease and into better methods of monitoring and treating the disease.

Recent Advances

Recently, an NIADDK-sponsored study was described in which the role of these circulating autoantibodies in the pathogenesis of pemphigus vulgaris was critically examined. Immunoglobulin G (IgG) fractions from five patients with pemphigus vulgaris were passively transferred into neonatal (Balb/c) mice. Thirty-nine of the 55 mice so injected developed cutaneous blisters and erosions that appeared histologically, ultrastructurally, and by immunofluorescence to have the features of pemphigus vulgaris as it appears in man. None of the 58 control mice given normal human IgG developed any of these lesions. The production of lesions was dependent on the dose of IgG given and the titer of pemphigus autoantibodies in the human donor. Furthermore, titers of circulating IgG in the mouse serum closely correlated with the extent of the disease induced. Thus, these studies present very convincing evidence that the circulating autoantibody in pemphigus vulgaris is directly involved in the pathogenesis of the skin disease.

Further support for the pathogenic role of pemphigus antibodies was provided by the recent report of transplacental transmission of pemphigus. In this report, a pregnant woman with pemphigus vulgaris under treatment with systemic corticosteroids gave birth to a stillborn infant with clinical and histologic evidence of pemphigus vulgaris. In addition, the infant's skin revealed bound intercellular IgG, and the umbilical cord blood was positive for intercellular substance antibody at 1:20 dilution.

These results make it possible to utilize circulating autoantibody titers more confidently in monitoring and treating patients with this disease, and to concentrate research on determining the method by which the autoantibody initiates the blistering process and on developing means by which this autoantibody production can be modulated in people afflicted with the disease.

Research Directions

Further research is necessary to answer a number of important questions in regard not only to pemphigus vulgaris, but also to other antibody-mediated diseases. Does the mechanism by which the autoantibody initiates the disease process operate by cell surface binding, enzyme activation, blockade of a normal inhibitor, release of hydrolytic enzymes, or other interactions? With this study, we now have an animal model of a human autoimmune disease in which these questions may be further investigated.

The Effect of Lipids in the Human Skin Water Barrier

Prior Findings

The stratum corneum is the outer horny layer of the epidermis. The normal human stratum corneum is an effective barrier to water loss from underlying body tissues. The portion of this layer most responsible for this impermeability to water was previously unknown, and this question has been argued for many years. Recent evidence indicates that the lipid portion of the stratum corneum is significantly involved; however, it has been only with two recent studies that this theory has been demonstrated quantitatively and correlated with defects in certain skin diseases.

Recent Advances

Researchers have demonstrated recently that stratum corneum cells from either the plantar surface of the foot or from the calf can be induced to reaggregate in the presence of lipids and form a coherent sheet of stratum corneum. This reformed stratum corneum sheet has been shown to be an effective

barrier to water penetration. The degree of water penetration observed was directly proportional to the amount of added lipid.

In a second study, scientists investigated this water barrier function using a group of recently identified lipids that are normally extruded by living cells in the formation of stratum corneum. These lipids, called sphingosines, are lost in essential fatty acid deficiencies, in which the barrier to water diffusion of the stratum corneum is greatly impaired. Scientists have demonstrated that this group of lipids is found in a regular pattern within a layer (lamella) of granules and that when these granules are extruded into the space between cells, the lipid is rearranged to form intercellular lamellae that lie parallel to and immediately below the horny cell envelope of stratum corneum. In this position, these lipids form the functional barrier to water diffusion.

Research Directions

These findings potentially provide a new mechanism for investigating the stratum corneum barrier to water in a number of skin diseases, predominantly those grouped as ichthyoses (characterized by scaly, "fish-like" skin). Further research is needed to determine what, if any, abnormalities in this lipid membrane exist in ichthyoses and other disease states in which the water barrier is abnormal. In addition, these findings may facilitate greatly the design of topical medications for the more efficient delivery of medications through this water barrier.

Vitamin D_3, Prostaglandins, and Sunburn

Prior Findings

Exposure to light in the ultraviolet burn (UVB) range causes both sunburn and the synthesis of vitamin D_3. The mechanism of sunburn reaction involves the prostaglandins. Vitamin D_3 production following ultraviolet irradiation is unique to the skin. These two mechanisms previously were thought to be independent of one another; however, recent evidence suggests that there may be an interrelationship between prostaglandin production and intermediates in the synthesis of vitamin D_3 following exposure to sunburn radiation.

Recent Advances

Recently, NIADDK grantees demonstrated that irradiated pro-vitamin D_3 activates the hydrolysis of labeled prostaglandin precursors. This is the first demonstration that local intermediates in the production of vitamin D_3 in the skin can regulate cellular processes in the epidermis. This work provides further insights into the pathogenesis of sunburn and biochemical reactions involved in the skin's response to UVB irradiation.

Research Directions

This work may foster further research into potential methods for intervention in the treatment and prevention of sunburn and long-term sequelae of excessive UVB exposure, including skin cancers and aging of skin.

Additional research is needed to determine which of the vitamin D_3 precursors are specifically involved in this reaction and exactly how they interact. Work is needed, too, on how the cyclo-oxygenase and lipoxygenase products of arachidonic acid, which are also part of this pathway, may be involved in UVB-induced inflammation, as well as in the melanin biosynthesis pathway and pigmentation.

Antibody-Dependent Cellular Cytotoxicity Implicated in Causing the Skin Lesions of Lupus Erythematosus

Prior Findings

Lupus erythematosus can affect skin alone, the skin in conjunction with multiple organ systems, or multiple organ systems with little or no skin involvement. Skin lesions in lupus may be short-lived, leading to no permanent scarring or may be long-lasting and, in some cases, result in scarring. There are numerous antibody abnormalities associated with lupus. Among them is a characteristic deposition (called lupus band test) of antibodies at the dermal-epidermal junction both in skin lesions of lupus and in normal-appearing skin of some patients with lupus.

The etiologic significance of this antibody deposition, whether it is of primary importance or a secondary phenomenon, has long been questioned. Several recent lines of research indicate that this antibody deposition does not cause the destructive skin lesions of lupus directly. It appears that the antibody is involved through an antibody-dependent cellular cytotoxicity that stimulates a T-cell-mediated reaction in the skin. Previous research has demonstrated that the deposition of immunoglobulin and complement in the skin of patients with SLE is unrelated to the classic skin lesions of lupus. In addition, studies of a number of specific antibodies to different cellular components also have failed to demonstrate any correlation with skin disease.

Recent Advances

Recently, evidence has been presented to demonstrate that the infiltrate in the skin lesions of lupus consists predominantly of T cells. Other studies have demonstrated that these T cells can be activated when target cells are coated with antibodies of the

types found in lupus. Finally, it has been demonstrated that this system functions when the target cell is in fact a keratinocyte, the predominant cell type in the epidermis and the site of injury in the skin lesion of lupus.

Research Directions

These findings have increased our understanding of how skin injury occurs in lupus erythematosus. Similar mechanisms may prove to be implicated in other immunologically mediated skin diseases, and therapies could be designed to impede this T-cell activity.

Further research is needed to examine larger numbers of patients to establish that this mechanism indeed causes skin injury in lupus. In addition, patients with other immunologically mediated skin diseases should be investigated to determine whether or not antibody-dependent cutaneous cellular cytotoxicity is involved. Finally, therapeutic interventions designed to interrupt this mechanism need to be developed.

The Mechanism of Cutaneous Delayed Hypersensitivity

Prior Findings

For many years the Langerhans' cell was a poorly understood cell residing within the epidermis (outer skin layer). Recent research has implicated the Langerhans' cell in delayed hypersensitivity (allergy) reactions. In previous studies, Langerhans' cells have been shown to act as antigen-presenting cells that stimulate the proliferation of antigen-specific cells. However, several other mononuclear cells with this capacity are also present in peripheral blood, and the specific role of the Langerhans' cell has been unclear.

Recent Advances

Recently investigators demonstrated that Langerhans' cells are more efficient than peripheral blood mononuclear cells in inducing antigen-specific cell proliferation. In addition, researchers demonstrated that well-known treatments for cutaneous hypersensitivity will inhibit Langerhans' cell activity. Treatment with ultraviolet light (and applying glucocorticoid drugs) has been shown to decrease the number or activity of Langerhans' cells. This finding suggests that the epidermal Langerhans' cell is the key cell in inducing delayed cutaneous antigen-specific hypersensitivity.

Recently a second pathway for the induction of contact hypersensitivity in the skin has been demonstrated in animals. This pathway does not involve Langerhans' cells, but can utilize an antigen presentation pathway independent of the Langerhans' cells.

Research Directions

Additional research is needed to trace carefully the chain of events in which the Langerhans' cells function. At this point, we do not know which of the various possible skin therapies most affect the Langerhans' cell in its interactions with the skin's immune system. It would be especially useful to know how the cell relates to the full range of hypersensitive skin diseases. In addition, we do not know the role of this cell in relation to treatments such as topical and systemic steroids, light treatment, or others that may affect this aspect of the immune system.

The Role of Keratin in Human Disease

Prior Findings

Keratins are a group of high-molecular-weight proteins formed in the epidermis (the outer layer of skin). Their organization into a regularly organized and densely packed structure forms the bulk of the stratum corneum, the dead layer of the human skin that acts as the main protection against both physical trauma and loss or gain of fluids through the skin. Much work has been done to elucidate the specific biochemical structure of various members of the keratin families and also the genetic basis for their inheritance. In addition, scientists have been investigating the question of control of the assembly of keratin into the structures found in the stratum corneum. There are great implications in this work for the evaluation of a number of dermatologic diseases characterized by specific and reproducible alterations in stratum corneum structure and function.

Recent Advances

In work on human epidermal keratins, the amino acid sequence for over 90 percent of the amino acids in one of the major forms of human epidermal keratin has been described. This is the first such filament protein to be described in man with this degree of completeness. These investigators have also been working to obtain the amino acid sequence for another (heavier) form of human epidermal keratin. With this specific epidermal structural information available, it will be possible to evaluate numerous human disease states of the epidermis to determine whether a structural abnormality in the keratin is produced in a disease state and also to evaluate how such a structural abnormality relates to a functional abnormality of the stratum corneum.

In some cases of human disease, the keratin structures may be normal, but they may be misassembled. Filaggrin is a protein found in human epidermis that functions in the assembly of keratin filaments in the formation of stratum corneum. Recent reports indicate that synthesis of filaggrin is present in excessive amounts in one form of ichthyosis (epidermolytic hyperkeratosis, a genetic disorder causing wart-shaped scaling and blisters). Further investigations are under way to determine whether filaggrin is abnormal in

quantity, structure, or function in a number of other human diseases.

Research Directions

Much work needs to be done in the investigation of the structure and assembly of the human keratins, both in normal and disease states. Once the structure and function of these macromolecules have been determined in the normal state, it should be possible to evaluate better the abnormalities in numerous diseases and to design treatment modalities specifically directed at remedying the resultant functional defects. It may also be possible to alter normal human stratum corneum more specifically in desirable ways, such as in delivery of drugs through the skin.

Immunologic Abnormalities in Vitiligo

Prior Findings

Vitiligo, or localized depigmentation of the skin, is a poorly understood disease affecting approximately 1 percent of the population. It may cause severe disfigurement, serious psychological stress, and interference with gainful employment. These difficulties are most noticeable and most severe among blacks and other darkly pigmented groups. The immediate cause of vitiligo is the destruction of melanocytes, the cells that make and bear pigment. They are completely absent in established areas of vitiligo and damaged in newly developing areas of the disease and at the margins of active lesions. The cause of the melanocyte destruction is not known. Melanocytes are found also within the central nervous system and in the eye, and their destruction in these locations sometimes occurs in association with vitiligo in the skin.

A large-scale cooperative study of vitiligo has been evaluating the wide range of clinical and laboratory manifestations in patients with this disease. This study has pointed out a number of previously unrecognized facts: (1) ocular involvement has been found in more than one-quarter of the patients with vitiligo, (2) conversely, patients with uveitis (inflammation of the uvea, which includes the iris, choroid layer, and ciliary body of the eye) have an increased incidence of vitiligo, (3) patients with both vitiligo and melanoma (a type of pigmented cancer of the skin) have better survival than patients with malignant melanoma without vitiligo, and (4) the use of oral psoralen drugs and high-dose ultraviolet A is the best available treatment, although its mechanism of action is still unclear.

Recent Advances

Recently, in other research, a new technique for demonstrating antibodies to surface antigens on normal melanocytes was applied to an investigation of a large group of patients with vitiligo. In this study, 81 percent of 51 patients with active vitiligo had antibodies to surface antigens of normal human melanocytes. This melanocyte-specific antibody is the first to be found in a high proportion of patients with active vitiligo independent of other well-known autoimmune diseases.

Studies utilizing the antibody assay, once validated, hold the prospect of determining whether autoimmune mechanisms are important in causing vitiligo or whether they simply are superimposed once melanocyte injury takes place from other causes.

Research Directions

Further evaluation of the specificity and pathogenic significance of these findings is necessary. In addition, further investigations of this finding regarding antibodies in the diseases associated with vitiligo, such as uveitis and malignant melanoma, may prove useful in the diagnosis and treatment of these diseases, as well as in the treatment or possible prevention of vitiligo itself.

Special Programs

Multipurpose Arthritis Centers

In 1974, the National Arthritis Act provided authority for the establishment of Multipurpose Arthritis Centers throughout the country. Each MAC has three components—research, professional and patient education, and community demonstration projects. Center funds are used to support pilot and feasibility studies in rheumatology-related areas that utilize innovative interdisciplinary scientific approaches to arthritis research problems. These projects supplement the traditional investigator-initiated research grants of individual workers associated with the center and may later form the basis of regular research grant applications.

Many exploratory or pilot research projects now under way could not have been started without the interaction of individuals brought together under the aegis and support of the arthritis centers grants. As the program has grown, increased support has been given to each center for innovative pilot or feasibility research projects that supplement the traditional investigator-initiated research grants of individual workers associated with each center. This research encompasses a wide range of disciplines and interests from basic biomedical research to health services research.

Several MAC's also conduct clinical trials to determine the safety and efficacy of new therapies for the treatment of arthritis. Because of the large number of arthritis patients available for study at the MAC's, they provide an ideal setting for closely monitored evaluation of new treatment regimens before dissemination and application among the general public.

Through computer- and telephone-based systems centered in certain MAC's, physicians who are not rheumatologists can obtain clinical consultations on arthritis problems in local areas, where the necessary expertise is not available. In addition to providing medical student training in the MAC's, the programs seek to improve rheumatic disease care given by primary-care practitioners. Selected centers also sponsor special programs, community projects, and model demonstrations of care in locations outside the center to increase public awareness of arthritis problems and to provide high-quality care. The coordinated approach to arthritis research and clinical care exemplified by the MAC program assures that the highest possible level of care is made available in a timely and effective manner for the benefit of the greatest number of people.

The annual evaluation report on the MAC program and center activities is presented in chapter VI.

Cooperative Systematic Studies in the Rheumatic Diseases

Research on treatment of rheumatic diseases is one of the major objectives of the Arthritis Program of the NIADDK. Studies on evaluation of drugs and drug toxicity are of particular importance in that patients suffering from the major rheumatic diseases are likely to require pharmacotherapy for many years. Well-designed systematic cooperative studies have yielded important information about the efficacy of antirheumatic drugs, and the requirements for such studies are expected to continue.

The investigations undertaken by this program are those highly unlikely to be performed by individual investigators, individual medical centers, or by pharmaceutical companies. They include definitive studies of promising new drugs, controversial treatments, and accepted, but unproven, treatments. Long-term studies by cooperating clinics, headed by a center with strong biostatistical expertise and data management, are meeting these needs.

Previous multicentered clinical trials have produced highly significant information on efficacy and risks of various agents (e.g., cortisone, gold salts, cyclophosphamide, d-penicillamine) in treatment of rheumatoid arthritis and have had major impacts on patient care.

Multicentered control trials that have been completed recently or are in progress include:

- Oral gold compound versus injectable gold salts in rheumatoid arthritis.
- Methotrexate in psoriatic arthritis.
- Pulsed methylprednisolone in lupus nephritis.
- Dimethyl sulfoxide (DMSO) in systemic sclerosis (scleroderma).
- Azathioprine versus d-penicillamine in rheumatoid arthritis.
- Low-dose methotrexate in rheumatoid arthritis.
- Classification and treatment of polymyalgia rheumatica.
- Early undifferentiated connective tissue disease.

Arthritis Information Clearinghouse

The Arthritis Information Clearinghouse (AIC) is a major component of the Arthritis Education Programs Office. The clearinghouse, established by the Institute on authorization by the National Arthritis Act and recommendation by the National Commission on Arthritis and Related Musculoskeletal Diseases, is completing its fourth year of pursuing its mission—to improve lines of communication among health professionals who provide care and related services to the arthritis patient.

The clearinghouse's major function is to collect, screen, store, and disseminate information about educational materials and programs on the rheumatic diseases. Additionally, the clearinghouse seeks to acquire better understanding of information needs of the providers of care, and especially of the unmet information needs of arthritis patients. These needs are communicated to the field nationwide, and support and technical assistance are provided to a network of information providers. Thus, by fostering the flow of arthritis information and by helping users to locate and select educational materials, the clearinghouse refers clients to appropriate information resources rather than acts as a distributor of the materials.

The clearinghouse has grown significantly in its 4 years of operation, both by introducing new educational materials and by expanding the more traditional lines of communication. The data base now consists of more than 2,700 records retrievable by key words, author, source, publication year, and text words in titles and abstracts. Included in the data base—which is now in place with an established mechanism for acquiring and processing these educational materials—are printed and audiovisual materials, journal articles, reports, and textbooks. Printed and audiovisual materials are being added to the data base as they become available. The identification and description of new educational programs and their incorporation into the data base are continuing priority functions of the clearinghouse.

Epidemiology Program

The Epidemiology Program provides an administrative core for efforts to encourage epidemiologic research in the fields of arthritis and musculoskeletal diseases. Epidemiologic studies of arthritis and musculoskeletal diseases contribute knowledge related to three concerns: assessing the community disease

and disability burden, studying the natural history of diseases, and investigating disease etiologies and identifying risk factors. Currently the portfolio of epidemiology grants includes regular research grants, training grants, an individual fellowship, and new and clinical investigator awards and contracts, at a cost of approximately $1 million. In addition, there are epidemiology projects within other grants, such as the Multipurpose Arthritis Centers.

Arthritis Data Systems Program

The Arthritis Data Systems Program fosters systematic acquisition, storage, retrieval, and analysis of information concerning the rheumatic diseases. Program effort is focused on assuring validity, confidentiality, and comparability of data collected in separate institutions, and integrating data resources with data needs. Rheumatic diseases data collection efforts and instrument development are prominent in three major settings: (1) American Rheumatism Association Medical Information System (ARAMIS), (2) Health and Nutrition Examination Survey (HANES I) Epidemiologic Followup, and (3) Multipurpose Arthritis Centers. Each of these programs is discussed in more detail below.

- *American Rheumatism Association Medical Information System*

  ARAMIS is a multi-institutional rheumatic diseases data bank system, funded by the NIADDK and administered from Stanford University, that currently contains data from 19,217 patients with 107,487 patient visits, representing 90,000 patient years of experience. The overall size of the data banks has increased by approximately 15 percent over the past year, and two new data banks are online. Data are gathered prospectively, and efforts to maintain long-term patient followup are vigorous.

  ARAMIS' goals include: improved diagnostic classification of rheumatic diseases, including establishment of acceptance criteria; identification of risk factors associated with good or poor patient outcomes, based on prognostic studies among defined patient subsets; and improvement of evaluation instruments for these purposes.

- *Health and Nutrition Examination Survey Epidemiologic Followup*

  In cooperation with the National Institute on Aging, the National Center for Health Statistics, and several other Institutes, the Arthritis Epidemiology and Data Systems Program participated in designing the instrument for collection of data in this resurvey of 14,407 individuals, originally sampled in 1971-75.

- *Multipurpose Arthritis Centers*

  MAC's continue to be active in the development, refinement, and application of health status measures, such as an Arthritis Impact Measurement Scale (AIMS), which detects small improvements in health. The MAC program is described more fully in chapter VI.

Program Accomplishments

Evaluation of the Musculoskeletal Diseases Program

The project to evaluate the Musculoskeletal Diseases Program was completed during 1983. Each task group provided a detailed report on the past activities and future recommendations for a segment of the program. The scientific areas addressed by four task groups were: basic bone properties and metabolism, bone disease and healing, articular joints, and other skeletal support structures and functions. A fifth task group considered the organization and management of the program. A steering committee report summarized the total project and provided an overview. Implementation concepts will be developed during the next year.

Clinical Trial of Fluoride for Osteoporosis

A clinical trial is under way to evaluate the safety and efficacy of fluoride in the treatment of osteoporosis. Over one-half of the expected 400 patients have been enrolled. Much baseline data on the risk factors and related disorders have been gathered in the recruitment phase. The anticipated outcome of reduced fracture incidence will require several years of data gathering.

Arthritis Information Clearinghouse

Daily scanning of journals and data bases to locate publications, audiovisuals, and meetings of interest has continued. Relevant materials have been acquired, cataloged, abstracted, indexed, and keyboarded for entry into the data base. The mailing list, which now includes approximately 5,000 names, has been updated and revised and names and addresses added.

- *Biblio-Profiles*

  The clearinghouse has initiated a series of Biblio-Profiles, short state-of-the-art presentations on a given topic followed by a bibliography. The level of the presentation (i.e., the target audience), its length, and its selective versus comprehensive nature are dictated by the topic and the anticipated use of the Biblio-Profile.

- *Cooperative Efforts*

  The Education Program Office and the AIC have continued to cooperate closely with all Federal and private components involved with arthritis. The clearinghouse continues to act as a depository for reports, reprints, and studies from the MAC's. A close working relationship also exists with the Subcommittee on Education and Training of the National Arthritis Advisory Board, with the education program office serving a key role in the preparation of various subcommittee documents. The Arthritis Foundation has joined with the clearinghouse in ensuring maximum cooperation in the dissemination of materials and joint exhibit displays at medical meetings. Similarly, the Education Program Office has discussed with the American Medical Association how the clearinghouse can interact with the AMA Medical Information Network. The office has also sought cooperation from the private sector, e.g., Upjohn Company and Merck and Company.

- *Other Clearinghouse Services and Products*

  Each month, the AIC handles 350 to 400 requests for publications, 100 to 120 mailing list additions, 20 to 30 data base searches, 40 to 60 referrals, general information and miscellaneous requests, and refers 50 patient requests to the Arthritis Foundation. The NIADDK Information Office handles more than 12,000 requests for the osteoporosis brochure each month. In addition to these services, the clearinghouse produces 40 bibliographies, reference sheets and catalogs; a thesaurus; cumulative catalogs of annual accessions; an audiovisual materials catalog; and patient education resources catalog. The clearinghouse distributes, each month, approximately 8,000 informational materials.

Epidemiology Research Program

The number of investigator-initiated research grant applications focused on epidemiology has continued to grow during the past year, although the rate of fundable applications remains low. A positive trend has been noted in the increasing volume of successful amended applications.

During the past year, two books were updated for publication: *Epidemiology of the Rheumatic Diseases* (proceedings of the Fourth International Conference) and *Epidemiologic Studies of the Rheumatic Diseases* (an annotated bibliography) and will be published in October 1983.

Examples of research accomplishments made possible by NIADDK support of epidemiologic activities have been given in the section on research advances. Two additional accomplishments are cited here:

One form of juvenile arthritis affects the small joints of the fingers and wrists. Splinting reduces pain and increases mobility of the hands. NIADDK programs such as the Arthritis Information Clearinghouse and the Multipurpose Arthritis Centers provide arthritis information, research, and training.

- There is a much lower incidence of rheumatoid arthritis among users of oral contraceptives than among nonusers.
- There are about 250,000 children with diagnosed juvenile arthritis, with a prevalence of about 1 case in 10,000 children.

Six of the MAC's have statistical and epidemiologic core units designed to enhance efficiency and effectiveness of the center's activities. The centers also help development of individuals skilled in pursuing epidemiologic studies of rheumatic diseases. In addition, epidemiologists familiar with other chronic diseases are being recruited. These programs may help to nurture the interest of young investigators in careers of rheumatic diseases epidemiology.

Arthritis Data Systems Program

The ARAMIS data system continues to play an active role in studies of rheumatic diseases classification and prognosis. Within the past year, both the revised SLE criteria and juvenile rheumatoid arthritis criteria were completed. Evaluation of the rheumatoid arthritis criteria was also completed. Other classification studies in psoriatic arthritis, seronegative rheumatoid arthritis, vasculitis, myositis, and osteoarthritis are in progress.

In one followup study by ARAMIS investigators, the Health Assessment Questionnaire was used to identify the predictors of future disability in moderate or severe rheumatoid arthritis patients. Three factors, radiographic grade, presence of symmetrical arthritis, and age of the individual, were found to be the most useful predictors of future disability of nearly 40 factors analyzed. Studies of long-term impact of disease on patients with rheumatoid arthritis are under way with regard to

mortality, disability, and cost. Preliminary findings indicate markedly increased mortality in rheumatoid arthritis patients and relate the increase in deaths to initial disease severity. Recent studies include the effect of methotrexate in rheumatoid arthritis and the effect of antihypertensive drugs in treatment of scleroderma. A questionnaire to measure side effects has been developed and is currently being validated. Another questionnaire, to measure both direct and indirect economic impact, has been completed and added to the ARAMIS outcome assessment protocols.

The followup of the Health and Nutrition Examination Survey has begun, and data collection for the extensive arthritis section has been free from serious difficulties. Plans are under way by the participating institutions to coordinate and cooperate in data analysis. In addition, plans have been made to follow the cohort for an additional time period.

Conferences

Conferences in research and clinical developments and advances in biomedicine facilitate the immediate exchange of information and cross-fertilization among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions. It is the fastest and most effective type of cross-fertilization process in biomedical research.

In 1983, the Arthritis Program supported five research conferences, totally or in part. Two were relevant to rheumatic disease and the others to skeletal muscle.

Partial support was provided to the Gordon Research Conference on Structural Macromolecules-Collagen held July 4-8, 1983. The emphasis of the conference was on the control of connective tissue production in normal and diseased states. The first four sessions were concerned with the structure, assembly, and normal turnover of collagens, adhesion proteins, and proteoglycans. The remainder of the sessions were concerned with mechanisms of control of production of connective tissue macromolecules, including regulation of replication of connective-tissue-producing cells, proliferative and fibrotic disorders, and hereditary diseases of connective tissue.

The program joined the National Institute of Allergy and Infectious Diseases to provide partial support for the Fifth International Congress of Immunology held in Kyoto, Japan, from August 17-21, 1983. The Congress is the fifth in the series of Congresses sponsored by the International Union of Immunological Societies; the last Congress was held in 1980 in Paris. These Congresses have grown in size and substance, have provided an important stage for the updating and reassessment of the burgeoning field of immunology, and have provided an important means of personal contact and communication among investigators in the field. This conference dealt with many important topics, including immunoglobulin genes and structures, cellular immunology, recognition units, membrane signals, immunoregulation, and transplantation immunology.

In conjunction with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the program contributed support for a Workshop on Voltage Clamping with Microelectrodes, held in Australia, on September 8-10, 1983. Two concurrent workshops were a Symposium on Synaptic Transmission and a Symposium on Smooth Muscle.

Finally, partial support was provided, again with the NINCDS, for a Gordon Research Conference on the Control of Muscle Contraction, held August 1-5, 1983. The primary emphasis of the conference was on the role of calcium and the sarcoplasmic reticulum in muscle contraction. This issue is important and central in the field; research has been moving rapidly. There are a number of state-of-the-art techniques for studying this role.

The National Arthritis Advisory Board, in cooperation with the Institute's Arthritis Program, sponsored a Prevention Conference on Arthritis, held July 19-22, 1983. The invited participants included a broad array of experts in the specific diseases discussed, such as osteoarthritis and rheumatoid arthritis, and the academic disciplines required to secure new knowledge. The aims of the conference were to: define opportunities for disease prevention in particular areas of arthritis, assess current knowledge content and deficiencies, develop prevention objectives, and construct strategies and specific actions to accomplish these objectives. The prevention conference was organized around workgroup meetings, in which the output of one set of workgroups was given to other groups for refinement. The resultant opportunities for prevention in rheumatic diseases are being compiled and will result in program initiatives.

The Musculoskeletal Diseases Program has organized and supported several workshops and conferences in fiscal year 1983. In a joint effort with the National Institute of Dental Research, a workshop was held at NIH on Local Factors Influencing Bone Formation. Twenty presentations were given by leading scientists, with resulting discussions involving many people from the audience of nearly 100. Highlights of the workshop included discussions of the development and clinical application of bone morphogenic protein, the identification of proteins that regulate bone formation, the differentiation of cell phenotype, and the electromechanical control of cell activity. A summary paper is in preparation.

In the fall of 1983, the program cosponsored, with the American Academy of Orthopaedic Surgeons, a Workshop on Bone-Implant Interface. The greatest

cause of failure for total joint implants is loosening at the bone-implant interface. Three possible substances are involved: the bone, the cement, and the implant. Detailed presentations and discussions were held on the mechanical and biological properties of and interrelationships between these components. A book will be published, by C. V. Mosby Company, based on papers delivered at the workshop.

The program supported the Gordon Research Conference on Bones and Teeth. The focus was on cellular control and function. Some of the sessions included: chemotaxis, angiogenesis, proliferation, differentiation, and hypercalcemia of malignancy. This open exchange of ideas provides for an important stimulation of future research.

The Skin Diseases Program contributed significant support to the 32nd Annual Symposium on the Biology of Skin, on the subject of Biology of the Keratinocyte *In Vitro.* Among the topics discussed were keratinocyte cultivation techniques, the ultrastructure of cultured keratinocytes, factors influencing growth or proliferation in culture, and techniques for separating keratinocytes from other epidermal cells, techniques for investigating the keratin gene, and aging of keratinocytes *in vitro.* The proceedings of this symposium will be published in the *Journal of Investigative Dermatology.*

The Skin Diseases Program cosponsored with the National Institute of Child Health and Human Development a workshop entitled "Morphogenesis and Malformations of the Skin." This 2-1/2-day workshop consisted of 32 presentations by various leading authorities in the field. The proceedings of this workshop will be published later this year. The Skin Diseases Program also supported a Gordon Research Conference on Epithelial Differentiation. The topics discussed at this conference included the areas of keratin mRNA and pseudo-gene molecular biology; synthesis, degradation and posttranslational modification of differentiation proteins; keratinocyte surface glycoprotein and receptor molecules and their modifying enzymes; the role of substrate attachment, adherence and proteinase in differentiation; and control of filament assembly by organizing centers and their role in complex tissue function.

The Skin Diseases Program sponsored a conference to update the report Analysis of Research Needs and Priorities in Dermatology. This conference was held in September 1983 and served to update the previous analysis, published under the same name, in 1979. The topics discussed were identical to that of the 1979 analysis, including chapters on psoriasis, eczematous and immunologic diseases, acne, malignant and benign neoplasms of the skin, and other important topics. This update is discussed further under "Program Plans."

Program Plans

Future Program Announcement—Rheumatoid Arthritis: Research on Causes and Mechanisms

Rheumatoid arthritis remains the major crippling disorder among the rheumatic diseases. The findings from research over the past few years make it more likely that rheumatoid arthritis is caused not solely by a single microorganism (virus, bacterium) or a deranged host factor, but rather by different agents generating immune responses that later lead to chronic inflammation in those with genetically determined abnormal immune regulation and biochemical abnormalities.

Many new basic research methodologies have been developed and are now available for finite experiments to test this and other hypotheses. These new technologies include monoclonal antibodies, recombinant DNA, and molecular biology. In addition, new experimental animal models have been developed, such as that induced by immunization with type II collagen. Utilizing these and other techniques, the following research areas can be investigated:

- Primary initiating events (triggering agents): viruses, bacteria, collagen, et al.
- Cellular basis of immune response: T- and B-cell maturation and subpopulations and interactions.
- The roles of idiotypes, anti-idiotypes and their immune complexes.
- Activities of lymphokines and monokines.
- Mediators of inflammation: prostaglandins, leukotrienes.
- Enzymes participating in joint destruction: collagenase, elastase.
- Molecular genetics, including mapping of the mixed histocompatibility complex.
- Correlative interdisciplinary research (of the above) to elaborate the kinetics of the pathophysiology of rheumatoid arthritis.

This broadly disseminated program announcement will serve to stimulate concerted research efforts capitalizing on these exciting new advances.

Program Announcement—The Need for Basic Research on the Role of Infections in Arthritis

The search for agents involved in an infectious etiology for arthritis needs to be continued and should include viruses and other latent or slow-acting microorganisms.

Because immunological factors play a major role in causing joint inflammation in rheumatoid arthritis and kidney and blood vessel inflammation in SLE, methods need to be developed for selective and specific suppression of those immune responses that mediate such conditions, but do not obliterate the body's defense against infections. The structure, function, and release of the mediators of inflammation, and the processes by which inflammation causes damage to joints and other tissues, should be better understood at the molecular level. Because genetic factors play an important role in predisposing to some of the inflammatory rheumatic diseases, high priority should be given to the search for new genetic antigens and to detailed epidemiological studies on the relationships between already known genetically determined tissue antigens and rheumatic diseases, such as ankylosing spondylitis and rheumatoid arthritis. Relationships involving antigens, immune responses, and the susceptibility to infectious agents should be further investigated to advance the knowledge of pathogenetic mechanisms. To understand the range of injury to articular cartilage from mild erosive changes to extensive destruction, more research should be conducted on the structure, function, biosynthesis, and normal metabolic turnover of large molecules in connective tissue that are degraded in arthritis. Further investigations should characterize patterns of degradation as compared to patterns observed in aging and normal metabolic turnover.

Program Announcement—Research Grants for Rheumatoid Spondylitis or Inflammation of the Vertebrae

These diseases include ankylosing spondylitis, Reiter's syndrome, arthritis of inflammatory bowel disease, psoriatic arthritis, and reactive arthritis.

The striking association between the genetic marker HLA-B27 and ankylosing spondylitis (95 percent) and related spondyloarthropathies (such as Reiter's syndrome, 75 percent) was established 10 years ago. Yet, the mechanism by which HLA-B27 exerts its role in pathogenesis remains obscure. Any hypothesis must account for the facts that not all B27 patients (approximately 20 percent) develop the disease and that a small percentage of Caucasians and a larger percentage of blacks with the disease do not possess HLA-B27.

Two major concepts have been advanced to explain this association. The first is that HLA-B27 by itself is unimportant; rather, it predisposes to the development of the disease, perhaps by modifying immune responsiveness. The second is that B27 itself is directly involved, in some way, as a facilitator or receptor for a triggering agent such as a bacterium or other environmental agent. Various infectious causes have long been suspected, but never established. Further work needs to be carried out to establish a possible role in ankylosing spondylitis for gram-negative enteric infections such as shigella, salmonellas, yersinia, and chlamydia. Also unresolved is whether or not the major genetic factor is HLA-B27 itself or a closely linked gene. An immunogenetics conference is planned to address this issue thoroughly and provide further specific direction to research activity in this area.

Several organisms have been demonstrated or proposed to be etiologic agents in Reiter's syndrome. The etiologic role of chlamydia in sexually acquired Reiter's syndrome needs to be settled. Putative pathogenic bacteria need to be subtyped, the association of particular subtypes with Reiter's syndrome tested, and the carriage of plasmids by putative pathogenic bacteria examined for disease associations.

A major recommendation of the Prevention Conference on Arthritis (see section on "Program Accomplishments") was an epidemiologic study to identify triggering agents, specifically a prospective cohort study in a high-risk group. This group would be families of HLA-B27-positive spondylitic patients with a large sibship of adolescent males, residing in areas of high exposure to putative infectious agents.

Several research grants will be awarded under this initiative, with the intent to determine whether, and if so, how, HLA-B27 or other related immunogenetic determinants predispose to spondylitic disease and to ascertain any role from gram-negative enteric or other organisms in triggering these diseases.

Program Announcement of Research Interest in Vascular Spasm and Scleroderma

Scleroderma, or progressive systemic sclerosis, is a chronic disorder characterized by diffuse fibrosis of the skin and internal organs. Dominant hypotheses concerning the etiology of systemic sclerosis (SS) center around vascular, connective tissue, and immunologic abnormalities. Immunologic studies have been concerned with lymphoid pathology, specific autoantibodies, and cell-mediated immunity. The connective tissue hypothesis suggests that scleroderma fibroblasts may play the primary pathogenetic role synthesizing excessive amounts of collagen even after multiple passages in tissue culture. Current interest is greatest in the vascular hypothesis because Raynaud's phenomenon is the first manifestation of scleroderma, often by years, and recent demonstrations by modern tracer techniques show that vasospasm (Raynaud's phenomenon) is responsible for the kidney, heart, and lung involvement of scleroderma. Serum factors directed to destruction of vascular endothelial cells have been discovered.

Recently, several new agents with diverse specific pharmacologic actions have been reported highly effective or promising in correcting the vascular

pathology of scleroderma. Treatment with captopril, the inhibitor of angiotensin I-converting enzyme, has proven lifesaving in scleroderma patients with malignant hypertension and early renal failure; digital ulcers have improved, perhaps from a bradykinin-like action of captopril. New calcium-channel-blocking agents, such as nifedipine, have been effective in combating Raynaud's phenomenon and scleroderma. In addition, there have been recent preliminary favorable reports of an antiserotonin agent, ketanserin, in treating Raynaud's phenomenon and scleroderma. With the help of basic research on the circulation and ascertaining the finite mechanism of action of these agents, there is promise of gaining new understanding of the etiology of Raynaud's phenomenon. Thereafter, the relationships between the vascular pathology and connective tissue overgrowth may be better addressed.

Attention is being devoted to pathologic changes taking place in the smallest peripheral blood vessels, or microcirculation. A program announcement will be issued to stimulate research on disturbances of the microcirculation and pharmacological interventions in Raynaud's phenomenon and systemic sclerosis.

Program Announcement on Viral Causes of Polymyositis

In the disease picture of dermatomyositis-polymyositis (DM-PM) there is muscle weakness, pain (myalgia), and inflammation (myositis) affecting multiple muscle groups in the body. Myalgia is commonly experienced in influenza-like illnesses and is probably due to inflammation of the skeletal muscles. An overt acute polymyositis has been recorded during and immediately following infection with influenza virus or with virologically undetermined influenza-like illnesses. This occurs in children where muscle biopsy may show either nonspecific myopathy or inflammatory cell infiltration with muscle fiber necrosis. A subacute polymyositis has also been described following rubella virus. Positive virological cultures from inflamed intercostal muscles have been obtained following Coxsackie virus infection, and an acute vascular myopathy has been reported with echovirus infection. Virus-like particles and rare instances of virological isolations have been reported in a number of cases with chronic polymyositis.

Two recent scientific presentations at national rheumatology meetings have escalated the likelihood that Coxsackie-B virus causes DM-PM. In one study, over 80 percent of sera from recently diagnosed children with DM had antibodies to this virus. In the second study, NIADDK investigators reported a model of polymyositis by inoculating newborn mice with Coxsackie-B1 virus. The animals developed proximal muscle weakness and histopathologic changes of myositis simulating those of human polymyositis.

An announcement will be made of program interest in this area of research, with the objectives to confirm Coxsackie-B virus as a cause of juvenile DM, to seek evidence for viral etiology of DM or PM in adults, and to investigate mechanisms of viral-induced muscle inflammation and destruction in a new animal model of polymyositis.

Workshops in Immunology as It Relates Directly to Rheumatic Diseases

Numerous advances have been made by rheumatologists in the areas of immunogenetics, immune complexes, immunopathology, and immunological expression of rheumatic disease in general. Understanding of the precise pathogenetic roles of immunological events in these disorders is still incomplete. Workshops are needed in these areas to bring together people working on various aspects of these phenomena and to relate what is known in basic immunology, both cellular and humoral, to the pathophysiology of specific rheumatic diseases. The exchange of ideas will stimulate, promote, and give direction to research in these important areas. Two workshops will be planned: one on immunogenetics and the other on immune complexes.

Encouragement of Research on the Epidemiology of Rheumatic Diseases

This will be a general program initiative with two objectives: to support the development of personnel to carry out needed research programs in arthritis epidemiology and to provide extra encouragement for investigator-initiated epidemiologic studies through existing support mechanisms.

Epidemiology is basically the study of distribution, transmission, and control of disease in populations. The application of this discipline to the study of rheumatic diseases is needed in a number of critical areas, including the magnitude of the disease and the disability burden that these diseases pose for the community. Factors associated with causation, risk, and prevention are, of course, central to dealing with these diseases and can be studied by epidemiologic methods. Few such recommended studies have been undertaken, and the number of skilled individuals trained in both epidemiology and rheumatology is very inadequate.

Epidemiologic studies were prominently encouraged at the July 1983 Prevention Conference on Arthritis sponsored by the National Arthritis Advisory Board in cooperation with NIADDK's Arthritis Program. The conferees proposed several promising research objectives: (1) define subsets of rheumatoid arthritis and identify prediction of disease outcome, (2) carry out population studies of rheumatoid arthritis

with respect to environmental factors, (3) continue osteoarthritis (OA) classification efforts, (4) identify risk factors for the progression of OA, including studies of the natural history, and (5) study the natural history of low back pain in both general and selected industrial populations, including the effect of psychosocial factors.

Program Announcement—Program Interest in Bone Cell Regulatory Factors

Major advances have been made in understanding of bone cell regulatory factors, and support for this work, along with initial studies in clinical application of these new developments, should go forward. The continuous remodeling of bone is a complex, multifactorial process. Several controlling proteins recently have been identified and isolated. These new leads should be pursued.

The Institute has supported several of the leading investigators in this area. A workshop on this topic was held at the NIH in the spring of 1983. Factors that regulate bone metabolism and remodeling were discussed indepth. Other factors that induce the formation of bone in gap areas were described. Current and future clinical applications were identified.

By stimulation of research interest in this area, this program announcement should contribute to the expanded base of knowledge required for future development of useful applications.

Program Announcement to Encourage Further Studies of Low Back Pain

Low back pain affects, in varying degrees, 8 of every 10 adults. Its total economic impact exceeds $10 billion annually.* The etiology of low back pain and its subsequent treatment are uncertain. In the majority of cases, a specific diagnosis is not determinable. The multitude of anatomic support structures and neurologic pathways have made it difficult to generate successful research projects. The Institute has supported only a small number of grants in this important area.

A workshop was held in December 1980 to encourage research, especially in multidisciplinary approaches. Subsequently, a few new grant applications were submitted, but more are required. The recently published book based on the workshop may provide a continued stimulus to the research community. Suggested research projects included studies of degeneration versus aging of the disc, development of mathematical and animal models, quantification of the types and functions of biological components of spinal connective tissue, evaluation of the distribution and function of nociceptors (pain receptors) in the spine, and identification of risk factors. A program announcement will be issued.

*American Academy of Orthopaedic Surgeons.

Program Announcement for Research on the Epidemiology of Scoliosis

This broadly disseminated announcement is intended to attract research grant applications in two areas: to develop means for early identification of individuals whose scoliosis will need treatment, while avoiding overdiagnosis and overtreatment of nonsignificant cases, and to elucidate the natural history and etiology of adolescent scoliosis of unknown origin.

Four to five percent of North American school children, ages 12 to 14 years, have scoliosis, defined as visible spinal rotational deformity on forward bending. Some spinal curvatures resolve spontaneously, some remain unchanged, and 3 to 10 percent will require bracing or surgical treatment. Progression may lead to unequal shoulder height, deformed waist, and unilateral back rib hump. Left untreated, severe scoliosis is associated with high frequencies of back pain and osteoarthritis, negative psychosocial sequelae, and an increased mortality rate. The etiology of scoliosis in the vast majority of cases remains unknown.

School screening for spine deformities in children in the United States has become fairly widespread, with a majority of states participating. Early diagnosis and treatment programs have been successful in reducing the number of large curvatures, and the need for surgical intervention has dropped significantly in many screening localities.

A serious problem remains with present screening efforts. Individuals whose spinal curves will need treatment cannot be differentiated from those whose curves will not progress. The latter incur unnecessary medical examinations, including X-rays, and high expenditures. Studies are needed that will define the characteristics of the child at high risk for developing disabling scoliosis.

Two epidemiologic study approaches for scoliosis were recommended by participants in the July 1983 Prevention Conference on Arthritis and will be encouraged under this announcement: (1) to delineate geographic and racial differences as to the incidence and prevalence of scoliosis, using uniform diagnostic criteria; the study should focus on determining environmental, geographic, or racial differences; and (2) to identify risk factors for both disease onset and progression through a prospective study design.

Consensus Development Conference on Osteoporosis: Treatment and Prevention

Osteoporosis is the leading bone disease in the postmenopausal population, with over 4 million peo-

ple afflicted to varying degrees. Epidemiologic studies estimate the economic impact of hip fractures caused by osteoporosis to be $1 billion annually. Several treatment modalities are currently at various stages of development and clinical acceptance. The Institute supports many projects directly related to osteoporosis. Two centers are now cooperating on a controlled clinical trial on the use of fluoride in osteoporosis; other studies deal with therapies such as estrogen, calcium, vitamin D metabolites, and exercise as preventive measures. An NIH consensus conference is being planned and organized by the NIADDK for 1984 to determine the state of knowledge and preferred current practice in osteoporosis treatment and prevention.

Workshop on Bone Mineralization

Mineralization is a key phenomenon in the development and continued remodeling of bone. Recent advances challenged previous theories. New types and distributions of extracellular components have been found. New proteins have been discovered that seem to regulate mineralization. Diffraction and nuclear magnetic resonance studies point to a less organized crystalline (not amorphous) initial form of hydroxyapatite. A workshop is being planned for 1984 that may generate new research ideas and be a broad stimulus to new efforts. Many projects have been supported in this area, with interesting outcomes, new technologies, and new theories. In some areas, controversial results and interpretations have led to the need for clarifying research.

Workshop on Bone and Cartilage Transplantation

A future workshop will assess current results with bone and cartilage transplantation and review methodologies. Special emphasis will be placed on immune suppression of tissue rejection and on surgical (microvascular) approaches. Replacement of damaged or diseased bones and joints with viable transplants may represent a long-lasting solution. The potential for application to younger patients is very significant.

Several research projects have been supported in recent years, but progress has been slow. New directions may be in the areas of histocompatibility, reduced immunogenic rejection, and microvascular enhancement. The planned workshop is expected to supply the direction and stimulation for new research activity.

Program Announcement—Oral Retinoids: Research on Mechanisms of Skin Effects

Oral retinoids are a very promising group of agents that have already received widespread attention and use in Europe and widespread attention but less widespread use in the United States. Retinoids are compounds based on the structure of vitamin A. They have recently been released by the Food and Drug Administration to be used in severe cystic acne. Studies in Europe have indicated that in one form or another retinoids are useful in the treatment of psoriasis and a group of keratinizing disorders. There are recent individual case reports indicating the retinoids may well be useful in several other diseases such as lupus erythematosus.

Investigations into the mechanisms by which the retinoids work have lagged behind the demonstration of their clinical efficacy. There have been recent reports demonstrating effects of retinoids in various tissue culture, organ culture, and animal model systems. Retinoids seem to suppress cholesterol synthesis in cultured human keratinocytes and have anti-inflammatory effects on human mononuclear and polymorphonuclear leukocytes. Further investigations into the mechanism(s) of action of retinoids are sought to identify other potential uses for these drugs and to investigate in detail both short- and long-term side effects. In addition, pharmacologic modifications will be needed to maximize the therapeutic efficacy.

Based in part on the results of an earlier workshop, an announcement of program interest in providing research support for work on oral retinoids in skin disease is being issued.

Program Announcement on Contact Dermatitis

The announcement under consideration in this subject area should serve to stimulate work on the following problems: the mechanism of primary irritant dermatitis, particularly in regard to industrial and environmental exposures; the mechanisms of initiation and elicitation of allergic contact hypersensitivity and methods for intervening either to prevent initial sensitization or prevent development of contact dermatitis; the inflammatory processes in both irritant dermatitis and allergic dermatitis; and atopic dermatitis, to determine how this disease relates to these other mechanisms.

There has been much interest in the role of the skin as an immunologic organ, particularly with respect to allergic contact dermatitis. Much of the current research in this area centers on antigen presentation in the skin, the role of the Langerhans' cell, and chemical intermediates produced during allergen processing in the skin.

There is also great current interest in the cascade of chemical events involved in inflammation. Much of the recent work in this field was presented at the 1983 meeting of the Society for Investigative Dermatology and published in the April 1983 issue of the *Journal of*

Investigative Dermatology. These new findings indicate directions for new research into mechanisms of allergic and irritant contact dermatitis, with potential for the development of new interventions in treatment and prevention of these problems.

Productive research in this regard would have a major impact on biomedical science in that the inflammatory process, mechanisms of sensitization, and the expression of delayed hypersensitivity are important in many diseases. In addition, occupational skin diseases, which are predominantly irritant in nature, are the largest single cause of industrial and occupational disease and have a huge national economic impact.

This program initiative will be in the form of a program announcement to emphasize the interest of NIADDK (along with two other NIH Institutes) in these areas of research.

Program Announcement on Drugs Effective for Skin Diseases

This program has two objectives: to apply new knowledge relating to the nature of the permeability barrier of the skin to the design and testing of new topically effective therapeutic agents and to apply new knowledge concerning distribution of therapeutic agents, and local activation by light or tissue-specific enzymes, to the design and testing of agents that would be effective only in the skin, without significant systemic effects.

Several skin diseases, including severe psoriasis, are treatable only with the use of potent systemically administered drugs, which may have significant and severe side effects. The skin is one of the most accessible organs and does have some unique enzymatic systems. Certain lipids (30 and 32 carbon atoms long) found in the intercellular spaces in the upper epidermis are key elements in the water barrier function of the skin; the lipids and the water barrier become abnormal in essentially fatty acid deficiency. In addition, orally administered psoralens may be activated locally in the skin by exposure to ultraviolet light and are then effective in the treatment of psoriasis and other skin diseases. Taking advantage of these facts should allow the design of therapeutic agents that are topically applied and are effective or are activated either by enzymes or externally administered agents such as light and thus would be effective only in the skin. This could have a great impact on the care of many of these diseases.

Genetic Skin Disorders Conference and Program of Research

The objectives of this conference would be threefold: to bring together for discussion people with various backgrounds in the investigation of genetic skin diseases; to review methods of identifying genetically determined skin diseases, such as disorders with DNA instability or chromosomal aberrations; and to discuss prenatal diagnosis of such disorders.

Recent advances in tissue culture technique and in evaluation of chromosomal abnormalities, DNA stability, and response to various external agents and recent discoveries of other markers for genetic diseases, including enzyme abnormalities, now make it apparent that it should be possible to diagnose either early in fetal life, or within families, the presence of certain of these diseases or the carrier state for these diseases. In addition, further investigation of these genetic diseases and the mechanism by which the abnormalities are expressed will give us much information concerning normal function. The ability to diagnose carrier states will be particularly useful in genetic counseling and in reducing the health-care burden of the country as a whole.

The Institute supports a number of research projects that look at individual aspects of this problem, such as DNA instability diseases, fetal tissue characterization, and tissue-culture-based research; however, these lines of research have not been brought together in a unified manner.

The objectives of this program initiative were assisted by a workshop entitled "Morphogenesis and Malformations of the Skin," cosponsored by the NIADDK and the National Institute for Child Health and Human Development, which was held in September 1983.

Survey of Research Needs in Dermatology: An Update

This effort would bring together a group of leaders in the field of dermatologic research to evaluate accomplishments and new areas of research that have developed since the publication, in 1979, of the original report on Analysis of Research Needs and Priorities in Dermatology.

The original report has provided the framework for much of the Skin Diseases Program planning since that time. Most of the material in that report was generated in 1977 and 1978, and thus is approximately 5 years old. There have been many advances in research in that time period, and therefore, a number of the items indicated in the original report as areas that needed investigation have already been investigated. Some of the areas that were underserved at that time remain underserved while others are now being supported, and because of the advances in the past 5 years, there are many new areas that were not even thought about in the original report that should be addressed.

Recognizing the need for this update, Congress mandated that the NIADDK support an update of this

analysis during fiscal year 1983. Therefore, the workshop was organized and preliminary data gathering completed during fiscal year 1983. The workshop was actually held in September at the end of fiscal year 1983; however, the preparation of the report to be presented to Congress and the final edition of the report of the workshop to be published in the literature will take place in fiscal year 1984.

III. Research Focus—Diabetes, Endocrinology, and Metabolic Diseases

Overview

The three major program areas comprising the responsibilities of the Division of Diabetes, Endocrinology, and Metabolic Diseases support the study of diseases that have devastating results in human terms. An example is diabetes mellitus, the fifth leading cause of death due to disease in the United States. Diabetes is characterized by a deficiency in insulin production or an impairment of insulin action. If the cells of the pancreas that secrete insulin are damaged, the loss of the hormone can lead to various other metabolic and endocrine disturbances that affect the regulation of the body's metabolism and may lead to widespread, chronic, degenerative lesions affecting every tissue of the body. If the mechanisms regulating the secretion or the action of insulin are defective, similar consequences can ensue.

Endocrine and metabolic diseases may be described as specific disorders that result in generalized malfunction of the body's systems for information processing. The information being processed may be derived from genetic coding, neural transmission, hormonal messengers, immunologic responses, or cell-to-cell communication. For example, if genetic information is miscoded, the result can be an inborn error of metabolism, such as cystic fibrosis. If the hormonal and hormone-like messengers of the body are malfunctioning, the result can be an endocrine disease affecting the whole body, such as dwarfism.

The intricate role of neuroendocrine messengers in regulating metabolic balance in the body provides a fascinating example of the interdependence of the body's communication systems. The mechanisms by which genetic and immunologic information is expressed in metabolism underlie much of the disease pathology with which the Division is concerned. The key to the successful treatment or cure of these diseases is the ability to correct the misinformation that is expressed or results in signs and symptoms of disease. At the present time, treatment measures often must focus on repeated replacements of an absent or abnormal hormone (a failed messenger), such as insulin, but NIADDK-supported research into basic mechanisms of these diseases could lead to measures that prevent or redirect the initial failure, permitting normal functioning of the body's systems to continue.

Diabetes

Diabetes mellitus is a complex disorder of carbohydrate, protein, and fat metabolism that affects an estimated 11 million Americans.* The diabetic condition can result in long-term complications that may involve virtually every tissue of the body, particularly the blood vessels, nervous system, kidneys, and eyes. Approximately 300,000 people with diabetes die every year; about half of these deaths are directly attributable to diabetes and its complications.* Since 1976, the economic costs of diabetes have doubled, in terms of medical care and losses due to

* National Commission on Diabetes.

A strong, inherited predisposition to diabetes is evident among the Pima Indians of Arizona. To gain a better understanding of diabetes, NIADDK scientists are studying genetic, environmental, and dietary factors that may contribute to diabetes and its complications in this homogeneous population.

Facing page

The development of portable insulin pumps enables people with insulin-dependent diabetes, like Bill Carlson (shown competing in the 112-mile cycling portion of the 1983 Ironman Triathlon), to administer the insulin they need in a continuous fashion and to adjust their doses for meals and exercise. NIADDK researchers are continuing studies to improve the safety and efficacy of insulin pumps and synthetic insulins.

disability and premature death. The financial impact of diabetes now exceeds $10 billion annually.*

In general terms, diabetes can be divided into two clinical types, with different prognoses, some differences in treatment, and causative mechanisms that are probably related but are dissimilar. The two types are called insulin-dependent (juvenile) diabetes (IDDM) and noninsulin-dependent (maturity-onset) diabetes (NIDDM). IDDM usually begins in early life—before age 40—and it is characterized by a requirement for daily insulin injections. Unless insulin is provided for the condition, patients will develop ketoacidosis, a buildup of acids and ketone bodies in their tissues and fluids, with a fatal outcome. Insulin-dependent diabetic people commonly experience greatly accelerated degeneration of blood vessels in many organs, which can lead to kidney failure, gangrene in the extremities, heart attacks, neuropathy, and blindness. Even with insulin treatments, the life expectancy of such patients is measurably shortened.

About 85 percent of all people with diabetes have the noninsulin-dependent form of the disease, which usually begins after age 40 and is characterized by a slower progression of the disease and its complications. Such patients usually do not develop ketoacidosis or require insulin. These individuals usually can maintain relatively normal blood sugar levels by adherence to prescribed diets, control of body weight, and use of oral agents to lower blood sugar levels. However, people with NIDDM also have a decreased life expectancy because of a variety of chronic vascular and neurological complications.

The Diabetes Program supports a wide range of fundamental and clinical studies related to the etiology, pathogenesis, diagnosis, treatment, and prevention of diabetes mellitus and its complications. Research in diabetes has brought remarkable advances in understanding and treating one of this Nation's most serious public health problems.

Endocrinology

The Endocrinology Program supports research into one of the body's major messenger networks. Investigations focusing on hormones—their roles and interactions in both health and disease—form the foundation of an extensive fundamental and clinical research effort.

Basic life processes, such as growth, metabolism, reproduction, and aging, rely not only on the amount of circulating hormone available, but also on factors within the target cells that influence the nature and intensity of the response. Moreover, a critical characteristic of the endocrine system is that few, if any, hormone-sensitive processes are regulated by a single hormone. Instead, several hormones appear to work in concert to effect and maintain body functions. Because these interactions are poorly understood, research is aimed at defining the nature of these interrelationships.

Endocrine diseases, such as thyroid diseases, adrenal and pituitary abnormalities, and growth disorders, are among the most common in medicine, and they have an enormous impact on individual well-being and the costs of medical care. Endocrine factors also play an important role in diseases that are attributed primarily to other organ systems, for example, atherosclerosis, cardiovascular disorders, cancer, and psychiatric disorders. For these reasons, the NIADDK supports basic and clinical research on the normal and abnormal functioning of the endocrine glands; the structure, function, and mechanism of action of the hormones produced; the effects of the hormones on various processes in the body; and the factors that relate to or modify the effects of the endocrine system.

Metabolic Diseases

Central to the Metabolic Diseases Program are studies related to the etiology, pathogenesis, and treatment of acquired and inborn errors of metabolism. Investigations in this area involve research related to enzymatic mechanisms, biological transport, and membrane structure.

Because the effects of hormones are manifested through metabolic events within the cell and because the endocrine system exerts the main regulatory influence on overall metabolism, the disciplines of endocrinology and metabolism have been intertwined and with them the field of genetically determined metabolic diseases. An important example of an inherited metabolic disorder with devastating effect on its patients is cystic fibrosis (CF)—a disease to which NIADDK traditionally has devoted considerable research support.

Although individual genetic disorders are not common, as a whole they have a profound public health impact. They account for approximately one-third of all infant deaths in the United States and approximately 30 to 40 percent of all admissions to children's hospitals. In addition, more than one-third of patients in state hospitals for the mentally retarded have genetically determined disorders, incurring costs for care in excess of $1 billion annually.

The NIADDK's mission in the area of metabolic diseases is to acquire an understanding of the etiology and pathogenesis of acquired or inborn errors of metabolism through support of a wide range of basic and clinical studies with the ultimate aims of improving their diagnosis, developing rational and effective methods of treatment and, where possible, achieving their outright prevention. Basic research is vital to the understanding of these diseases and in-

*National Commission on Diabetes.

cludes the study of normal metabolic processes and the fate of metabolic fuels such as lipids and amino acids.

Highlights of Research Advances

The following section briefly highlights a number of areas in which the Division of Diabetes, Endocrinology, and Metabolic Diseases has reported recent progress in its research programs.

- One type of resistance to insulin in people with diabetes may be due to loss of ability to recruit an adequate supply of glucose-transporting molecules from the center of the cell to the interior aspect of the cell membrane. Resistance may also be associated with a defense in the synthesis of such transporter molecules.
- Nine out of ten insulin-dependent diabetic people have detectable genes of the type that convey susceptibility to the disease; testing for these genes eventually could permit identification of people at risk for diabetes.
- Noninsulin-dependent (type II) diabetic people have a characteristic type of insertion of genetic material next to the insulin gene on their chromosomes. Although not part of the gene coding for insulin, these insertions could alter insulin gene expression. Study of this insertion could provide the long-sought marker for type II diabetes, allowing identification of those at risk early in life, so that a preventive regimen of weight control and exercise could delay or abort emergence of the latent disease in advanced age.
- A pituitary hormone affecting insulin secretion by the pancreas has been discovered in obese mice and man and given the name B-cell-tropin.
- Improvements have been made in the techniques for transplantation of pancreatic tissue to elaborate insulin in diabetic laboratory animals and in the design of implantable devices for administration of insulin.
- Initial clinical trials of human growth hormone (hGH) produced by genetically modified bacteria confirmed that its effects and potency are identical to those of pituitary hGH, both in children and in adults, and that it is free of side effects.
- The hypothalamic hormone that regulates release of pituitary hGH has been extracted (from pancreatic tumors), analyzed, and synthesized, and its activity appears identical to the natural hormone. It can be produced in large amounts and will be useful in treatment and in diagnosis.
- A long-term trial has shown that children with hypofunctioning parathyroid glands, and consequent low blood calcium levels (which can lead to tetany and death), can be treated safely and effectively with the hormonally active metabolite of vitamin D_3, 1,25-dihydroxyvitamin D_3.
- An inhibitor of ovarian function in laboratory animals has been discovered. It antagonizes the hypothalamic hormone controlling pituitary release of the hormones controlling the ovary and has potential for use in treatment of certain tumors and of precocious puberty, as well as in fertility regulation.
- Part of the mechanism of the defect in the sweat gland in cystic fibrosis was further clarified. Permeability of the glandular lining membrane to reabsorption of the chloride ion appears to be decreased, resulting in passive loss of both chloride and sodium into the sweat of CF patients.
- A method for identifying carriers of the gene for maple syrup urine disease has been developed. Previously, there was no way to identify suspected carriers of this inherited metabolic disease, and thus, genetic counseling to avoid pregnancies that could result in infants with this devastating disease (which is the case when both mother and father are asymptomatic carriers) was not possible.
- The molecular basis for the inborn defect in cystinosis has been identified as a defective mechanism for energizing the elimination of cystine from lysosomes (intracellular enzyme reservoirs) of cells throughout the body. Accumulation of cystine in lysosomes in the kidney leads to renal failure.

Diabetes Research

Insulin-Dependent Diabetes Mellitus: Causes and Development

Prior Findings

In insulin-dependent diabetes mellitus (IDDM or type I diabetes), there is structural or functional damage to the insulin-producing cells (beta cells) of the pancreatic islets (insulin-secreting cells), resulting in complete dependence on administered insulin.

Considerable evidence indicates a major role of an immunologic component early in the development of

IDDM. Evidence of immune response in islet tissue (insulitis, with lymphocytic infiltration) has been documented in patients who died during the first several weeks or months after the onset of IDDM. Antibodies to islet cells, as well as a growing list of antibodies against other elements of the endocrine system, have been identified in most IDDM patients at the onset of the disease.

One present theory holds that some environmental insult (such as infectious agents or chemical substances affecting the cell) triggers the disease in those people who are genetically predisposed and consequently have a vulnerable immune system. It is hoped that by using some method of controlling or altering the immune system in highly susceptible persons, the beta cells can be saved from destruction. Early recognition of the process, before the appearance of cell damage and hyperglycemia, is essential.

Some epidemiologic evidence has accumulated that implicates viral infections as possible etiologic or provocative factors in the initiation of the beta cell inflammatory response leading to IDDM. In animals, it has been possible to prevent the development of virally induced diabetes by vaccination with nondisease-producing strains of the diabetogenic viruses.

Recent Advances

The serum of diabetic children contains an antibody specific to pancreatic islet cells and seems to have autoantigens, which cause such antibody production, against their own pancreatic tissue. It now appears that genetic coding associated with the disease process occurs on chromosome 6 (HLA sites DR3 and/or DR4, among the histocompatibility genes) and seems to convey susceptibility to the disease. Testing for these genes permits identification of people at risk for developing diabetes; about 90 percent of IDDM patients have them.

It has been demonstrated, through HLA typing, that siblings and other first-degree relatives of children with IDDM have increased risk for development of the disease. Such individuals may have islet cell antibodies several years before development of clinical disease. In one case of twins where one was diabetic, the second developed the disease 36 years later—with the appearance of antibodies 5 years before onset. Such findings have led to description of IDDM as a chronic autoimmune disease of insidious onset.

As further evidence of the role of immunologic mechanisms in diabetes, an immune-response antigen, designated the "Ia-antigen," is detectable on the T lymphocytes (thymus-derived immune response cells) of most individuals with IDDM. Increased numbers of Ia-antigen-bearing T cells are found in other autoimmune diseases as well. This antigen is also coded by a gene in the HLA region of chromosome 6 (in humans). As a rule, T cells express the Ia-antigen only if stimulated by another antigen or by a substance inducing cell division (a mitogen).

In a related study, a substance stimulating mitosis in T cells (a mitogen, concanavalin A) facilitated the experimental production of severe diabetes, with inflammation of the islet cells (insulitis), in young diabetes-prone rats that received spleen cells from diabetic rats of the same strain (BB/W). Spleen cells alone or in combination with lymph node cells were able to transfer the disease to the nondiabetic animals. This passive transfer is evidence of cell-mediated autoimmune mechanisms in the cause of IDDM in these animals. The same investigators also found that weekly transfusions of whole blood from a nondiabetic subline of BB/W rats prevented the development of spontaneous diabetes and insulitis in susceptible BB/W rats.

Molecular genetic mechanisms affecting the expression of the insulin gene represent another area of major advance and are discussed below under "Biological Synthesis of Insulin."

Research Directions

The following research efforts are important for further understanding of the causes and development of IDDM:

- The gene products of the HLA antigens should be identified, and the specific genetic elements in the HLA region of chromosome 6, which may be associated with beta cell destruction, should be determined.
- Prospective studies of the natural history of IDDM prior to the development of clinical symptoms, and of the factors (including genetic features) that contribute to the clinical onset of the disease and its complications, should be carried out.
- The role of viral infections and other external agents as etiologic or provocative factors should be established, and their relationship to specific HLA types and beta cell destruction should be evaluated.
- The role of the immunologic components in possible pathogenetic mechanisms should be elucidated.
- Risks and potential benefits of immunosuppressive therapy in the prevention of the clinical onset of IDDM should be evaluated.

The Mechanism of Action of Insulin

Prior Findings

Metabolic derangements associated with diabetes mellitus may result from any of several abnormalities, including a decrease (or complete lack)

in the amount of available insulin, a change in the structure of available insulin, or an alteration in the action of insulin on its target tissue. Insulin is concerned primarily with controlling the storage and metabolism of the three major metabolic fuels—carbohydrate, protein, and fat. This control occurs principally in liver, muscle, and adipose tissue. Metabolic alterations at the level of these target tissues are influenced not only by insulin, but also by various other hormones that counter the action of insulin, such as peptide hormones (glucagon, growth hormone, and peptide growth factors), steroid hormones (cortisol, estrogen, and progesterone), thyroid hormones, and catecholamines. In fact, it is the delicate balance between insulin and these other hormones that controls blood glucose levels in man throughout the day. For each of these hormones, biological activity results from interaction of the hormone with a receptor on the outer cell membrane, transduction of the hormone signal across the membrane, and a sequence of intracellular events that carry out the metabolic effects of the hormone by influencing the activity of one or more regulatory enzyme systems. Until recently, very little has been known regarding the processes that follow the interaction of insulin with its receptor.

Recent Advances

The crucial action of insulin in recruiting glucose transport molecules from the interior of the cell to the plasma membrane is discussed in the section on "Insulin Resistance."

The nature of the interaction of insulin with its receptor has been studied by NIADDK intramural scientists and by grantees. In what may be a very early event in insulin action, insulin is able to phosphorylate (add phosphate to) one of the two major protein subunits in its own receptor. The phosphorylation of proteins is known to be an important regulatory mechanism in hormone action; the receptor phosphorylation could initiate a cascade of other phosphorylation steps leading to insulin's effects in the cell. The phosphorylation could also play a role in the regulation of receptor affinity for the hormone, or in "down regulation" of the number of receptors, or alter the rate of internalization of the receptor (and hormone), or modify the generation of "second messengers" involved in hormone action.

Evidence that insulin-responsive cells internalize the insulin-receptor complex and process it further internally has been obtained. This study was done by comparing cells sensitive to insulin (fat cells and connective tissue fibroblasts) with cells unresponsive to the hormone (IM-9 human lymphocytes in tissue culture) and localizing the radiolabeled insulin in the interior of the responsive cells. The nonresponsive cells shed the insulin-receptor complex into the incubation medium, with no internalization.

The full array of insulin's metabolic effects in cells still remains to be defined. A recent study has shown a direct link between insulin's association with its receptor in liver-cell cultures and the effect on a specific messenger ribonucleic acid (mRNA) that codes for a key enzyme involved in the synthesis of glucose, phosphoenolpyruvate carboxykinase (PEPCK). This observation suggests that the insulin-receptor interaction may be coupled to the activity of insulin in controlling glucose synthesis (gluconeogenesis). The evidence seems to indicate that insulin decreases mRNA and thus decreases glucose synthesis.

A new finding is that an endogenous peptide called beta-endorphin has an effect that counters the action of insulin. The endorphins are called opiate-like because of their actions in the body, sharing the same receptors as opiate drugs. They are released into the blood (along with ACTH, from the pituitary) under certain conditions, such as stress, but are produced also in the pancreatic islets and may have local effects on the endocrine pancreas. Small doses of beta-endorphin increased blood glucose concentration in diabetic and normal subjects, preceded by a rise in glucagon level. In the nondiabetic people, it also increased insulin level. None of these effects could be blocked by a drug that negates effects of opiates (naloxone), probably because they make use of a type of receptor resistant to naloxone blockade. The endorphins appear to have a role in blood sugar counterregulation (anti-insulin), mediated at least in part by glucagon.

Research Directions

Many aspects of the various phases of hormone action need further study. The application of new tools and ideas will continue to provide important insights into the events involved and should provide new strategies for the treatment and amelioration of diabetes and its complications. Increased efforts are needed to define the exact nature of hormone receptors and their turnover, to isolate and purify the second messenger(s), to clarify the role of various factors such as cyclic AMP and calcium in the mechanism of hormone action, and to further define and characterize the nature of insulin resistance.

Specific research opportunities may be summarized as follows:

- The exact structure and amino acid sequence of receptors must receive attention and may provide important clues concerning the mechanism by which insulin regulates cell function.
- Increased efforts to define the earliest steps in insulin action, especially characterization of the active sites and enzymatic nature of the insulin receptor complex, should be made and should allow development of strategies to mimic or

modify insulin action at the cellular level. They may lead to simple, orally active insulin-like agents.

- Further studies of insulin action on tissues involved in diabetic complications, particularly vascular endothelium, are needed.
- More detailed understanding of the process of insulin degradation and receptor turnover is necessary and may allow development of selective inhibitors that could enhance hormone action.
- Studies of the distribution of insulin following secretion or peripheral injection are desirable and may help define differences in metabolism between the insulin-treated diabetic and the nondiabetic populations.
- Studies are needed to define further the postreceptor defect responsible for insulin resistance in NIDDM.

Insulin Resistance in Diabetes and Noninsulin-Dependent Diabetes Mellitus

Prior Findings

Noninsulin-dependent diabetes mellitus (NIDDM, or type II diabetes) is characterized by hyperglycemia (elevated blood sugar level), usually associated with obesity, and usually controlled by diet restrictions, exercise, and when necessary, by administration of either oral hypoglycemic (blood-sugar-lowering) drugs or insulin. One of the strongest risk factors for NIDDM is obesity; a lean body weight and exercise appear to have a protective effect against development of the condition. The development of NIDDM is further complicated by the decline in glucose tolerance seen with normal aging.

Evidence for a strong genetic input in the development of NIDDM exists, although no definitive markers have been identified. As in IDDM, there is evidence for the involvement of environmental factors.

Although IDDM is characterized by a lack of insulin, NIDDM is characterized by resistance to the action of insulin in body tissues (an inability of the hormone to contribute to cell metabolism by the normal process). NIDDM patients appear to have an impairment of insulin's ability to enhance glucose intake and metabolism in target tissues, thereby causing an accumulation of glucose in the plasma. Insulin resistance may reflect alterations in the insulin receptor on the surface of target cells, in insulin secretion, and in intracellular glucose metabolism. There appears to be a pancreatic defect in insulin secretion, as well as a defect in insulin action, in some NIDDM patients.

Recent Advances

Insulin increases the rate at which glucose transport molecules from inside the cell bind glucose from outside the cell by increasing the number of these molecules at the binding site (more are shifted from storage pools within the cell), within a few minutes of insulin exposure.

In NIDDM, and in the obese, insulin is less able to translocate glucose-transporting molecules to the cell's surface membrane. The availability of fewer such molecules in the storage pools, in diabetic and obese people, would explain the observed decrease in insulin's ability to stimulate effective glucose transport into cells.

Other recent work has assessed the effects of high-fat/low-carbohydrate feeding on glucose transport activity and has shown that (maximally) insulin-stimulated glucose transport activity decreases, due to a decrease in the number of glucose transporters in cell membrane protein and also in the intracellular pool. This decreased activity suggests a selective reduction in the net synthesis of glucose transporters. These findings may reflect a general systemic impairment in insulin action and may provide an explanation for insulin resistance.

Diabetes can result if the insulin molecule secreted by the pancreas is itself defective. An NIADDK grantee has now identified a defective gene causing synthesis of abnormal insulin and has localized the precise coding error corresponding to a single faulty amino acid in the insulin molecule, called a "point mutation." The patient had hyperinsulinemia, but was unable to use the insulin, due to the defect, and developed diabetes. The normal molecular site for recognition of the enzyme that cleaves the insulin gene (a restriction endonuclease enzyme) had been lost. Two additional mutant insulins with differing coding errors have now been discovered, in other patients.

Research Directions

The following research efforts should be pursued:

- Further studies are needed on factors that increase risk for development of NIDDM in genetically susceptible individuals (e.g., obesity, physical activity, age, and diet).
- Definition of the relationship between defects in insulin secretion and insulin resistance is necessary, to determine whether the (eventual) reduced insulin secretion in type II diabetes results from high output failure (secondary to compensatory, intensified secretion of insulin to overcome the existing insulin resistance) or if insulin resistance develops secondary to a primary defect in (abnormally high) insulin secretion.

- The effects of exercise on cellular-level events leading to NIDDM need amplification.
- Further evaluation of drugs that might influence insulin receptor activity and postreceptor events, and could alleviate insulin resistance, is desirable.

Biological Synthesis of Insulin

Prior Findings

Advances in our knowledge of gene structure and expression and recombinant DNA technology continue to have a dramatic impact on biomedical research in many areas related to diabetes. Highly purified insulins, which are now commercially available, appear to reduce allergic reactions in diabetes. Human insulin, made in bacteria by recombinant DNA techniques, has been studied extensively and is already available, thus ensuring a continuing adequate supply of insulin for the world's population.

Recombinant DNA techniques have allowed structural studies of the human insulin gene. A gene consists of a combination of coding and noncoding nucleotide base pairs. Each nucleotide has a 5′ and 3′ end; when they interlock to form a sequence, the newly formed sequence then has a 5′ and 3′ end. The 5′ end is thought to contain the promoter, the end at which messenger RNA transcription is initiated. The coded message contained within the structure of this gene is transcribed by a complex process that ultimately results in the synthesis of insulin. Molecular engineering technology has provided chemical probes for the analysis of DNA and RNA structure, function, and regulation; this analysis is useful for a better understanding of the synthesis of insulin and other hormones related to all forms of diabetes. Most important, these approaches to studying DNA and RNA and the findings from the studies have immediate application in all genetically influenced diseases. Using such new methods, it is now possible not only to look at the sequence of base pairs that carry the primary message of the gene, but also to study deletions of base pairs and insertion areas, which are base pairs in or near the gene that do not carry its primary message.

Recent Advances

Investigators under NIADDK support studied variations in insertion areas in and around the 5′ (or promoter) end of the human insulin gene. This group found considerable variability at the 5′ end of the gene; these variations correlated with the race of the individual and the type of diabetes, NIDDM or IDDM. The existence of these insertions near the promoter end of the gene suggests that they may play a role in insulin-gene expression and could cause altered gene expression under certain conditions.

A possible mechanism of abnormal insulin-gene expression in NIDDM was identified: insertions in the DNA chain near the 5′ end of the nucleotide molecule were found in two-thirds of the NIDDM patients tested (compared to 29 percent of nondiabetic people tested). These insertions were several thousand base-pairs long and could play a role in interfering with normal expression of insulin synthesis.

Most recently, it was discovered that NIDDM patients had a characteristic type of insertion, independent of race; this region was 1,600 nucleotide bases in length and accounted for 80 percent of the observed variation in types of structure (based on length) at the 5′ end of the insulin gene. It is possible that this finding may ultimately provide the long-sought marker for NIDDM, enabling those at risk to be identified early in life so that rational adherence to preventive lifestyles (avoidance of obesity, regular physical exercise) could prevent the emergence of the latent disease.

Another study performed by a Danish group examined this same area of the insulin gene (including the insertions) in 47 NIDDM patients and 93 controls (other diabetic and nondiabetic subjects). DNA was isolated from nucleated blood cells, and two distinct classes of insertions were identified in the region of the insulin gene. The larger size class was designated "U," and the smaller size class was designated "L." Each individual has a pair of genes (alleles, on corresponding chromosomes) for this characteristic, so that the genetic combinations (genotypes) of the different individuals were either UU, LL or UL. Results showed an increased frequency of the larger insertion area (UU) in NIDDM patients (6.3-fold increase) as compared to IDDM patients, indicating that the size of this insertion may be a potential genetic marker for NIDDM.

Research Directions

The new techniques already developed could identify those at high risk for developing diabetes. These techniques should be extended to include studies of other hormones as well. On the basis of recent accomplishments, several new initiatives are now possible and should be pursued:

- Further improvement in genetic screening for diabetes based on gene analysis is now possible in populations at risk.
- More work is needed to develop a complete picture of the control of expression of the insulin gene, including the role of variable and multiple sequences in the gene structure.
- More study is needed of the genetic structures associated with synthesis of other hormonal and neural substances important in diabetes.

The Process of Insulin Secretion

Prior Findings

Considerable progress has been made in clarifying the specific molecular events and cellular processes by which specialized endocrine cells secrete peptide hormones (including insulin) and by which such secretory processes are controlled. In this regard, it has been determined that abnormally high levels of circulating insulin are characteristic of some types of diabetes and of obesity. Attention has focused recently on the altered mechanisms that control insulin secretion in these conditions.

The study of pancreatic islet hormone secretion has led to a number of findings of great importance to the field of diabetes. For example:

- The pancreatic islet is a complex organ composed of at least four cell types, each secreting a different hormone: B cell—insulin; A cell—glucagon; D cell—somatostatin; and pancreatic polypeptide-secreting cells.
- The secretory activities of the various types of islet cells are modulated by a diverse group of protein hormones (particularly from the gastrointestinal tract and the brain) and neurotransmitters (via the autonomic nervous system).

Recent Advances

Because the pituitary gland secretes a number of hormones that regulate the activity of various other endocrine glands, investigators have long sought a peptide from the pituitary that might affect insulin secretion in the pancreas.

In one recent study, an extract from the intermediary lobe of the pituitary of ob/ob mice, animals that are genetically obese and have abnormally high levels of insulin (hyperinsulinemia), has been shown to stimulate insulin release when used as a perfusate in an isolated rat pancreas preparation. This extract was also shown to stimulate fat synthesis in cultured adipocytes (fat cells). A factor with similar activity has now been identified in the plasma of ob/ob mice and in 4 of 10 obese humans, but not in lean controls. These results suggest the possible involvement of an insulin secretion-inducing hormone from the pituitary in hyperinsulinemia associated with obesity. This factor has been named B-cell-tropin (BCT), and work is in progress to fully characterize it. Clinically oriented studies are planned to assess whether diet and fasting affect the insulin-releasing activity of this factor and to establish whether or not there is a relationship between the hyperinsulinemia found in diabetes and obesity and BCT activity.

A recent study of cells derived from rat islet tumors has produced evidence suggesting that the function of islet cells may be directly regulated by the activity of other islet cell types. If these results obtained from tumor cells can be generalized, they would indicate that as islet cells become specialized with regard to the hormones they secrete, they may also become different from each other in the receptor binding patterns that they display. Such differentiated binding patterns would be consistent with a local (paracrine) type of control of hormone secretion. Studies of this type may shed some light on the actions of islet cell hormones on normal cells within the islets.

Research Directions

Specific issues that merit further study include:

- The integration and quantitative contribution of various metabolic, hormonal, and neurologic factors involved in regulating insulin synthesis, storage, and secretion must be clarified.
- The availability of animal models with genetic or experimental aberrations in insulin secretion should be increased.
- New methods should be developed to assess islet cell function and control, in both diabetic and nondiabetic human subjects.

Transplantation of Pancreatic Tissue to Treat Diabetes

Prior Findings

A conceptually attractive method for treating the lack of insulin production seen especially in IDDM involves replacement of the defective pancreas or islet cells of the pancreas, by transplantation of normal tissue. A major practical problem with these procedures involves the rejection of the transplanted tissue by the host's immune system. Prolonged suppression of the immune system usually has been necessary, but this can cause additional complications. Transplantation of the whole pancreas has not been particularly successful, due in part to its rejection by the new host and in part to the problem of secretions from its nonendocrine glands—the exocrine glands—which secrete a digestive-enzyme-rich fluid into the small intestine via the pancreatic duct.

Recent Advances

New techniques have been developed that can prolong the survival of transplanted rat pancreatic islet cells across major tissue compatibility (strain and species) barriers by procedures that do not require continued administration of immunosuppressive agents. In general terms, these procedures involve diminishing the lymphoid cells that cause activation of cyto-

toxic (cell-killing) T lymphocytes (white blood cells active in tissue immunity) and rejection by the host.

Techniques for whole pancreas transplantation have been developed that involve the injection of synthetic polymers into the pancreatic duct to ablate the exocrine function. The use of a silicone rubber adhesive coupled with extraperitoneal placement of the tissue to absorb residual secretions has resulted in some success in human patients who have already committed themselves to daily immunosuppression because of receiving a kidney transplant. Nevertheless, graft rejection is still a major problem, and despite advances in immunosuppressive therapy (e.g., the new drug cyclosporine), the applicability of this approach continues to be limited.

Research Directions

All possibilities relating to the successful transplantation of the pancreas islet cell must be explored. The ability of such transplants to normalize carbohydrate metabolism and prevent complications in humans needs to be established precisely. The laboratory procedures that have prevented rejection of islets in rats and mice should be applied to islet transplantation in larger animals and should be extended to fetal and human islets. Immunologic studies concerning the mechanism of the rejection reaction and the means to suppress it should be expanded. New techniques for islet encapsulation to prevent immunorejection are required. The importance of the anatomic site of islet cell transplants needs to be determined.

Devices for Delivery of Insulin

Prior Findings

Previous methods for administering insulin by injection have not permitted precise control of blood glucose on a minute-to-minute basis throughout the day; this has led to attempts to develop mechanical devices to achieve the necessary control. Automated insulin delivery systems have been designed, but the problem of incorporation of a sensor for blood glucose concentration has resisted solution. Significant progress has been made in instrumentation for delivering insulin in a more physiological fashion, permitting near normalization of the blood glucose level for prolonged periods in persons with diabetes.

Now that many of the mechanical and technologic aspects of insulin pump development have been solved, more attention has been focused on the problems of insulin aggregation (clumping) as well as on mode and site of hormone delivery and the social impact on patients of the various insulin delivery devices.

Recent Advances

One new type of implantable device now being developed contains a cluster of insulin-secreting animal islet cells. These cells are separated from the bloodstream by a semipermeable membrane that allows passage of smaller molecules, such as glucose and insulin, but blocks passage of larger molecules, such as those involved in immune rejection. Such a device, if it can be perfected, would have several advantages: it would deliver insulin and other islet-derived hormones in response to changes in blood glucose levels; it would not require immunosuppression; and it would permit use of islets of animal origin, which are in plentiful supply.

One of the major limitations in developing mechanical insulin pumps for implantation has been the aggregation of most regular insulins into insoluble clumps that gradually block the flow of insulin from the pump. Various approaches have been attempted to overcome this problem (solvents such as glycerol, additives such as bicarbonate). One group has successfully used sulfated pork insulin, which is more resistant to aggregation than other insulin preparations used, in their infusion pump. They have demonstrated markedly improved glycemic control using the sulfated insulin versus regular insulin.

The feasibility of an intraperitoneal (intra-abdominal) insulin delivery device in IDDM patients who were nonresponsive to subcutaneous insulin was recently assessed by investigators using a device implanted subcutaneously, adjacent to the umbilicus, with its delivery catheter terminating in the peritoneal space. Three patients who had repeatedly suffered from uncontrolled diabetes, in spite of large doses of subcutaneous insulin injections, and thus were incapacitated in their ability to work, were implanted with this device with encouraging results.

Intensive insulin therapy is associated with acute lowering of blood sugar (hypoglycemia) from excess insulin in some patients. A test was developed under NIADDK support to identify those people with IDDM who are at risk of neurologic or other complications of hypoglycemia. A standard dose of intravenous insulin was infused, at a standard rate, at the bedside. Careful clinical assessment and frequent blood glucose estimates, under these conditions, successfully identified patients without adequate glucose counterregulation after the insulin dose. The inadequate response is due to the combined effect of deficiencies in the two hormones glucagon and epinephrine, frequent in IDDM patients.

Research Directions

- Increased efforts are needed to develop reliable glucose-sensing devices not only for closed loop

pump systems, but also for use with self-monitoring and portable insulin delivery systems.

- Continuation of research is necessary to define the optimal quantities, routes, and timing of insulin delivery required to normalize the diabetic patient's metabolism.
- Efforts to develop smaller external and implanted pumps with appropriate safety features, which would allow for more widespread use of these devices, are desirable.
- Efforts to develop more stable insulin preparations and better biologically inert catheters for insulin delivery to the tissue site, both compatible with insulin pumps, should be made.
- Development of precise noninvasive methods to assess the extent of the microvascular, macrovascular, and neurological complications in diabetic patients is needed.
- Multidisciplinary assessments—not only of the clinical benefits, but also of the psychosocial, toxicological, morphological, functional, and financial side effects of newly evolving therapeutic modalities—are highly desirable.

The Diabetes Program has continued to support the development and evaluation of both extracorporeal and implantable automated insulin delivery systems for use in biomedical research. The program's contracts for the development and refinement of insulin delivery systems have generally met their stated goals and are now being phased out. As these projects have moved to completion, private industry has expressed considerable interest in further refining and marketing some of the devices previously developed by the program under contract.

The Complications of Diabetes

Prior Findings

Diabetic patients at any age have mortality rates far higher than those for the general population because of the complications of diabetes. These complications are similar in both insulin-dependent and noninsulin-dependent diabetes, affecting primarily the large and small blood vessels, kidneys, eyes, and nerves.

Most physicians and scientists believe that the complications of diabetes appear to be related to the effects of the chronic derangement of metabolism at the tissue level; however, this relationship has yet to be established unequivocally in man. The blood vessel abnormalities are of two distinct types: microangiopathy and macroangiopathy. Microangiopathy, or the degenerative changes of small blood vessels, is an underlying cause of diabetic retinopathy and kidney disease. Macroangiopathy affects the large arteries and can result in myocardial infarctions, cerebrovascular disorders, and peripheral vascular disease (such as obstruction of the blood supply of the legs). Research into the causes of the complications, as well as their treatment, prevention, and cure, is a fundamental part of the overall effort to combat diabetes.

Recent Advances

One recent study of kidney pathology focused on thickening of the glomerular basement membrane (GBM), part of the filtration apparatus (the glomerulus) of the kidney. This study demonstrated that diabetic glomerular pathology can be documented within 1 year of onset of experimental diabetes in the dog and suggests that the improved glycemic control resulting from continuous insulin infusion prevents the development of GBM thickening.

In experimental diabetes, there is a slowing of nerve conduction, possibly due to accumulation of certain carbohydrates (sorbitol, fructose) in peripheral nerves. A new drug called Sorbinil is a potent inhibitor of the enzyme involved in these changes for this effect. During 9 weeks of daily treatment, patients with stable diabetic control and no signs of nerve pathology showed greater nerve conduction velocity in all three nerves tested (both sensory and motor nerves) than during a 9-week period without the drug. Within 3 weeks of stopping the drug, conduction velocity for all three nerves decreased significantly. These effects did not relate to control of blood sugar, which remained unchanged during the study.

Impotence in diabetic men, which may be due to peripheral nerve pathology or other causes, can be compensated for quite successfully by use of implanted penile prostheses. A questionnaire followup was sent to 127 patients who had received such implants. From 107 responses, the satisfaction rate among patients and their sexual partners was 81 percent and 83 percent, respectively, with increased frequency and enjoyment reported by those in the satisfied groups. Postoperative complications were treatable, for the most part, and the procedure could be recommended for patients not sexually compromised by other physical or emotional conditions. Impotence occurs in 50 to 60 percent of diabetic men.

Fecal incontinence and diarrhea are particularly common in long-standing diabetes complicated by neuropathy (nerve damage or dysfunction). In a group of 16 patients, incontinence was found to be related to abnormal internal anal sphincter function (lowered internal sphincter strength) and was associated with signs of autonomic nervous system pathology (such as impotence, hypotension, and sweating) and in some, with steatorrhea (fatty stools). The external anal sphincter pressure was normal. Those without diarrhea had normal sphincter pressures and were not likely to develop later incontinence.

Research Directions

Further studies are needed to assess the relationship between the metabolic state in the diabetic person and the development of complications. The cause and mechanism of glomerular basement membrane thickening in diabetics and its relationship to impairment of organ function need to be determined.

The relationship between the earlier functional changes in the diabetic kidney and the later development of morphological alterations and kidney failure needs to be elucidated. Methods and treatment strategies are needed to delay the need for dialysis and transplantation.

The mechanism of accelerated macrovascular changes in patients undergoing hemodialysis must be elucidated.

The usefulness of Sorbinil and other similar agents in the prevention or treatment of neural degenerative changes should be tested in larger clinical trials. The relationship of abnormalities in nerve conduction velocity to the clinical symptoms of nerve damage must be established. Further studies of the roles of insulin and glucose in both central and peripheral nervous system metabolism are needed. Nerve biopsy materials from patients with diabetes and animal models demonstrating diabetic neuropathy are required to permit more detailed studies of the pathogenesis and treatment of this complication. Studies of other abnormal findings in diabetic neuropathology are clearly needed, not only to determine their significance and pathogenesis, but also to identify ways in which these abnormalities may be modified or prevented.

Endocrinology

Growth Hormone Synthesis by DNA Techniques

Prior Findings

Growth hormone, which is produced by the pituitary gland, is necessary for normal growth in children. Some children lack this hormone and do not grow unless they receive it by injection. The only source of the hormone to date has been human pituitary glands collected at autopsy. With the advent of recombinant DNA technology, however, the human gene for growth hormone has been isolated and inserted into bacteria, which are now producing the hormone.

There has been continued progress related to the production of human growth hormone by genetically modified bacteria. Much of the basic research underlying this development was supported by the Endocrinology Research Program and reported in previous years. Bacterially produced hGH is now being manufactured by a commercial company. Published reports show that the synthetic hGH causes growth in test animals indistinguishable from that caused by natural hGH. In addition, clinical trials in humans have been initiated.

Recent Advances

An initial clinical trial in adult volunteers has confirmed that the hGH produced by recombinant DNA technology is as potent as pituitary hGH and is without significant side effects in short-term use. The initial study was too brief to show any growth of cartilage, bone, or soft tissues, but it is continuing. Meanwhile, an initial clinical trial in children in several centers has shown a threefold increase in the growth rate of 22 hGH-deficient youngsters from ages 4 to 16, a rate of progress comparable to that of children receiving the human-source hormone. The recombinant DNA product produced low antibody levels, like those seen with the hormone from human pituitaries, but the development of antibodies did not interfere with the growth-promoting effect or cause any complications or safety problems. Studies to date have shown that the new product reproduces all of the metabolic effects of pituitary hGH and is indistinguishable from it. Its use made possible the verification of one effect of hGH that previously had been disputed—a breakdown of fatty tissue resulting in increase in serum lipids (triglycerides)—attributed by some to hGH contamination with other pituitary proteins.

The Institute's National Hormone and Pituitary Program (NHPP) is collaborating with the private sector in this important project by supplying natural hGH to use as control material for tests on the purity and antigenicity of bacterially produced hGH.

Research Directions

When hGH produced by bacteria becomes available for routine use, a fully adequate supply will be available to treat short-stature children; but, it should also be available for use in other clinical studies involving accelerated healing of bone fractures, burns, and ulcers. Although hGH affects processes other than growth, research on its other effects has been delayed because most of the hormone has been used in clinical research on short stature.

The Releasing Hormone for Growth Hormone

Prior Findings

Crude hypothalamic extracts, when injected into experimental animals or when added to pituitary cell cultures, cause the release of various pituitary hor-

mones. On the basis of this observation, endocrinologists have hypothesized that the hypothalamus secretes releasing hormones, which serve to control the secretory activity of the pituitary gland. Several of these releasing hormones have been characterized and synthesized: thyrotropin-releasing factor (TRF), which stimulates pituitary secretion of thyrotropin-stimulating hormone; gonadotropin-releasing factor (GnRF), which stimulates release of luteinizing hormone and follicle-stimulating hormone; and corticotropin-releasing factor (CRF), which stimulates secretion of the adrenal-stimulating hormone (ACTH) and beta-endorphin, an endogenous opiate-like substance.

For many years, the releasing hormone for the pituitary's growth hormone (GRH) has been sought in the hypothalamus. The extremely minute quantities involved have prevented definitive identification and characterization of GRH in the hypothalamus, although its inhibitor (somatostatin) has been discovered there.

Recent Advances

Peptides with the biological activity of hypothalamic GRH can be produced, in rare clinical cases, by human pancreatic islet cell tumors. Two recent studies from the same institution, but from different laboratories, now report on the structure of GRH. In both cases, the hormone was extracted from pancreatic tumors. Patients were discovered to be developing acromegaly (gigantism, or abnormally increased growth), but no pituitary abnormalities could be found; however, tumors were discovered in the islets of the pancreas. When removed and tested, the tumors were shown to be producing a substance that caused release of GH from the pituitary. This material has now been extracted, purified, analyzed, and synthesized, and its biologic activity has been assayed and compared with extracts from the hypothalamus. The conclusion drawn is that the material from the tumors is very similar to, if not identical with, hypothalamic GRH.

The material extracted by one group has 44 amino acid residues and appears to be a complete polypeptide hormone. The other group has extracted a peptide of which the first 39 amino acids are identical to those found by the first group, and the 40th is probably the same. The second group found only 40 amino acids in its material. In both cases the material is highly active biologically.

Research Directions

The obvious advantage to having this material characterized is that it may be useful therapeutically. For example, short stature in some children may be caused by failure of the hypothalamus to secrete GRH rather than an inability of the pituitary to produce GH. Use of GRH (or some analogue) may well replace the need to treat some children with GH.

Application of GRH (along with other releasing factors) can be developed into clinical assays of the pituitary's ability to secrete the corresponding hormone. (Absence of response to any of the releasing factors indicates pituitary disease or tumor.) Production of the relatively small GRH molecule in large quantities will now be possible. Clinical investigation is expected to begin in the near future. The action of GRH will be explored in animals and humans. Analogues will be sought that have different activities and lengths of action. Analogues or antagonists may have some value in treatment of some cases of acromegaly.

Treatment of Hypoparathyroid Children With Vitamin D_3

Prior Findings

Calcium uptake and metabolism by the body is controlled by three hormones: 1,25-dihydroxyvitamin D_3 (1,25 $(OH)_2D_3$), which controls calcium uptake from the gut into the bloodstream (and affects bone mineral mobilization and bone mass, in a manner as yet unclear); parathyroid hormone, which mobilizes calcium from bone, increasing the blood calcium level; and calcitonin, which tends to lower the blood calcium level and therefore is antagonistic to PTH. Lack of parathyroid hormone causes symptoms of decreased blood calcium concentration, with ultimate tetany (muscular contractions and tremors) and death. Treatment of hypoparathyroidism involves efforts to keep the blood calcium level at near normal levels.

Parathyroid hormone has been successfully synthesized by researchers at the National Heart, Lung, and Blood Institute; and NIADDK grantees have cloned the gene for the precursor (preproparathyroid) hormone into the bacterium *Escherichia coli (E. coli)*. These researchers have used the clones for studies on the structure of the hormone as well as on the structure of the gene itself. Because clones are available, the production of large amounts of preproparathyroid hormone should be possible in the near future, enabling expanded research efforts in numerous areas of endocrinology and metabolism. Intramural scientists at the NIADDK have contributed extensively to work in this area.

Because parathyroid hormone is currently in short supply and must be injected daily to be used therapeutically, other methods of treatment have been sought. Vitamin D and high dietary calcium have been used; however, it has been discovered in recent years that 1,25 $(OH)_2D_3$ is a more active form of the vitamin.

Recent Advances

A research team supported by NIADDK reported the use of 1,25 $(OH)_2D_3$ in 10 children with

hypoparathyroidism, for a total of 35 patient years. The patients were kept normocalcemic with daily ingestion of the vitamin and adequate calcium in the diet. There was no indication of resistance to the vitamin. Monthly blood testing indicated that minor changes in blood calcium level could be corrected by changes in the amount of 1,25 $(OH)_2D_3$ ingested.

Although this vitamin had been used in treatment previously, this was the first long-term study that showed that this method of treatment is safe and effective. Basic research on the mechanism of action of vitamin D helped to discover its biologically more active form (which acts like a hormone) and thus made this improved therapy possible.

Research Directions

Continued studies on parathyroid hormone are needed to give greater insight into its method of action and to make it available for clinical treatment in greater amounts.

Identification of an Orally Active Inhibitor of Ovarian Function

Prior Findings

Luteinizing-hormone-releasing hormone (LRH) is secreted by the hypothalamus and controls the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland. Because LH and FSH control ovarian function, antagonistic analogues of LRH may be useful as contraceptives. Several LRH antagonists have been developed, but because they must be injected, their use for contraception is limited.

An analogue of LRH has been shown to be effective in the short-term treatment of precocious puberty. Puberty is initiated by the pulsed nocturnal secretion of gonadotropins (LH and FSH), which results from the episodic release of LRH. This process begins prematurely in precocious puberty, but can be reversed by daily injections of the LRH analogue for 8 weeks.

Recent Advances

Recently, NIADDK-supported investigators discovered an LRH antagonist that was extremely potent but short acting when injected into rats. As little as 5 micrograms caused complete inhibition of ovulation for a few hours. Because of its high potency, the antagonist was tested for activity when ingested. When mixed with an inert carrier and an enzyme inhibitor (to help prevent breakdown in the gastrointestinal tract), 2-milligram doses completely inhibited ovulation for the duration of the estrus cycle, with lesser doses being proportionately less effective.

Research Directions

Not only is it possible that LRH antagonists may prove useful as contraceptives, but they also may prove useful in therapy of prostatic tumors, precocious puberty, and other disorders where it is necessary to interrupt sexual function. If the studies of this analogue in animals continue to yield promising results, clinical studies in humans may be undertaken. Work will continue to identify and produce other hormone analogues with potentially useful properties.

A New Method for Measuring Adrenal Glucocorticoid Hormones

Prior Findings

The adrenal cortex produces three major types of hormones, concerned with sugar metabolism, mineral balance, and sex-hormone blood levels, respectively. The first of these are called glucocorticoids.

Glucocorticoid hormones (cortisol in man) provide for adaptation to changing environmental conditions—collectively known as stress. Cortisol is a major hormone involved in gluconeogenesis, whereby energy stored in fat and muscle tissue is mobilized for conversion by the liver to the readily usable energy source glucose. Cortisol synergizes with other hormones to provide for cardiovascular, muscular, renal, immunological, and other system adaptations to adverse conditions. Cortisol has actions on virtually every cell type in the body. The hormone is required for basal function and for the action of other hormones of these cell types.

In large amounts, cortisol has suppressive effects on immunological and inflammatory responses, and these actions are the primary reason for the widespread therapeutic use of cortisol in disease processes that do not directly involve the adrenal gland. In order to reduce deleterious side effects, the lowest possible dose consistent with the therapy must be given. A problem in measuring glucocorticoid levels in patients receiving steroid therapy arises in assessing simultaneously the cortisol produced in the body and the administered steroid. The problem is that several assays must be employed to determine the levels of the various steroids, both natural and injected. Since only unbound glucocorticoids are biologically active, an assay method that would measure free glucocorticoid activity in the plasma would be useful.

Recent Advances

A method has now been developed that measures the free levels of plasma cortisol and any compound that binds to glucocorticoid receptors. The method uses rat pituitary tumor cells grown in tissue culture. Because only the free steroids in plasma are able to bind

to the receptors, bound steroid is not measured. Because it uses radioactive steroid compounds and the cell receptors, the method described is a radioreceptor assay.

There are several advantages to this assay method. First, the assay detects any steroid that has glucocorticoid activity. Several steroids are often used in therapy, and this method can detect them all. Second, the assay can detect a combination of active glucocorticoids all at the same time. Third, the assay is sensitive to free steroid rather than to total steroid concentration in the plasma. The free steroid is the active steroid, so the only compounds measured are those available to the body. This assay should prove very helpful in monitoring steroid levels in patients on steroid therapy. The assay is simple and fairly rapid.

Research Directions

This practical application illustrates the use of basic biological techniques in clinical medicine. Further studies on the mechanisms of hormone binding and action will give greater insights, and other practical applications are to be expected. Clinically, studies on the effect of various steroids in therapy should be done in order to determine which hormones have the greatest therapeutic effect in various diseases and disorders.

Pituitary Hormone Release Cycles: Control by the Hypothalamus

Prior Findings

Both growth hormone (GH) and thyroid-stimulating hormone (TSH) are released by the pituitary in response to releasing and release-inhibiting factors from the hypothalamus. The release of both hormones is episodic, with the GH release pattern in male rats characterized by a cycle of about 3-1/2 hours. It is believed that GH secretion is stimulated by GH-releasing hormone (GRH) and suppressed by somatostatin, a peptide in the hypothalamus.

Release of TSH also fluctuates during the day. Its release is stimulated by thyrotropin-releasing hormone (TRH) and is suppressed by somatostatin also, in all probability.

Recent Advances

In an effort to understand why GH and TSH are produced in a cyclic fashion, rats were injected with endotoxin (a bacterial product). The endotoxin caused both GH and TSH blood levels to fall to very low values and to remain there as long as endotoxin was present. There was no sign of cycling of the hormone levels. The day following endotoxin treatment, GH and TSH were again being produced, but in larger amounts than normal and not in a cyclic fashion. Eventually, cycling returned.

In a second experiment, rats were injected with antiserum (antibodies) to somatostatin 4 hours after injection of the endotoxin. The antiserum caused a large increase in GH production almost immediately after injection. It also caused an increase in TSH secretion. The conclusion was that endotoxin caused a large increase in somatostatin secretion, which resulted in the suppression of both GH and TSH release from the pituitary. This conclusion is supported by the antisomatostatin studies. The increased release of both GH and TSH after the effects of endotoxin have worn off probably is due to either a decrease in the stored amount of somatostatin available for tonic control of both hormones or to a decreased sensitivity of the cells' receptors.

In experiments using somatostatin antiserum, another team of researchers discovered that the antiserum does not inhibit the pulses of GH production. They hypothesize that GH pulsations may be produced by pulsatile secretion of GRH from the hypothalamus.

These studies give insight into the cyclic nature of hormone production and secretion. They offer further indications of the control of endocrine function by the brain. The periodic pulsing from specific areas of the brain, with its hormonal effects, underlies daily biological rhythms. Data have also been obtained concerning the effects of endotoxin on the body and on the endocrine system, thus affording clinical insights.

Research Directions

Experiments are being done to decide which rebound hypothesis is the correct one. Also, since rat and human systems do not always react the same, similar studies should be done in primates before clinical applications are attempted.

Further research is needed on neuroendocrine mechanisms of biological cycles or clocks (circadian rhythms), of major importance to human sleep, eating, and sexual patterns and functions.

Thyroglobulin: Gene Structure and Cloning

Prior Findings

In vertebrates, thyroid hormone is produced and stored in the thyroid gland as the result of the coupling of iodotyrosine (thyroxine) molecules to a large glycoprotein. The resultant molecule, thyroglobulin, is one of the largest globular proteins of the body. Knowledge of the structure of this large molecule would help us to understand better the causes of

various thyroid defects, such as a goiter and hypothyroidism.

Recent Advances

Using the method of reverse transcription (from the specific RNA back to the original DNA), the DNA sequence for the bovine thyroglobulin gene has been determined. Portions of this gene have been cloned also in *E. coli*. Four clones have been made, and the researchers believe that together these clones represent 99 percent of the bovine thyroglobulin structural gene (which contains 8,000 nucleotides, or bases). The availability of the cloned thyroglobulin gene means that the entire structure of the bovine thyroglobulin molecule now can be determined.

The same research group has isolated messenger RNA for human thyroglobulin. Cloning in *E. coli* of complementary DNA (cDNA) developed from mRNA has resulted in determination of 41 percent of the structure of the human gene for thyroglobulin.

Research Directions

The availability of cloned human thyroglobulin cDNA fragments now permits the isolation and characterization of the corresponding DNA segments of the gene itself. Congenital defects of thyroglobulin production may then be studied.

Work will continue to obtain the total and exact structure of the thyroglobulin genes in these and other species. Chromosomal localization of the gene also will be undertaken. Ultimately, knowledge produced by studies such as described here will give us detailed information on the molecular defects that may cause congenital goiter. This knowledge may then be used to treat the disease.

The Family of Pituitary Growth Hormones

Prior Findings

Human growth hormone as extracted from the pituitary gland is not a single substance—it consists of several molecular forms. The predominant form is a single-chain peptide of some 190 amino acids (and a molecular weight of 22,000), called hGH-B. Several two-chain forms also are found (hGH-C, -D, and -E), derived apparently by cleavage of the basic molecule. Two of these (hGH-D and -E) are actually more potent than hGH-B, which suggests that hGH-B may represent a pituitary storage form, serving as a "prohormone," which is activated by cleavage before and during secretion to its biologically most active forms.

A smaller single-chain variant, 15 amino acids shorter, is present also and is designated as 20K-hGH (because of its molecular weight of 20,000). It exhibits properties somewhat different from the usual hGH. It has been found that 20K-hGH stimulates both growth (in the rat) and somatomedin production. The somatomedins are a family of small growth-promoting peptides related to insulin; their action is linked to that of growth hormone. Unlike other hGH, the 20K-hGH is inactive as a diabetogenic substance (it did not cause glucose intolerance or hyperinsulinemia in studies using dogs). Limited proteolytic digestion of the molecule did not generate diabetogenic activity, although it does generate such activity with regular hGH. This variant has been found in some normal human pituitaries, and thus, it is considered to be a part of the family of pituitary growth hormones.

Recent Advances

To gain insight into the chemical nature of secreted hGH, researchers have studied the synthesis and secretion of hGH by human pituitary glands in organ culture. One normal pituitary and five pituitaries from patients with pituitary disease (acromegaly, prolactinemia, Cushing's disease, and chromophobe adenoma) were studied. hGH secreted into the culture medium was examined by physical methods as well as by immunochemical criteria. In all cases, the predominant form secreted was hGH-B (22,000 molecular weight, intact chain). Cleaved two-chain forms of hGH, and 20K-hGH, were below the detection threshold (less than 5 percent of all hGH).

From these experiments, it was concluded that, in the test tube, the pituitary secretes primarily the single-chain hGH-B form and does not cleave it to the more active forms before or during secretion. In addition, it was found that in acromegaly the hGH secreted by the pituitary is indistinguishable from the hGH of the normal person.

Research Directions

Understanding the physiologic role of each isohormone of hGH may lead to more effective treatment of hormonal disorders involving growth. Because these are test-tube experiments, additional studies should be made in the living organism to determine the type of hormone produced. It is possible that different types of hGH may be secreted, depending on the metabolic needs of the organism, and this possibility should be investigated.

Like many other hormones in the body, growth hormone has been shown to have a variety of physiologic effects in addition to the stimulation of cell and tissue growth. It has been suggested that these various effects may be caused by different types of growth hormone. Such heterogeneity may occur either because several genes produce growth hormone products that vary slightly from each other, or because growth hormone as it is known now is converted into different biologically active fragments when it is utilized by

various organs and tissues. With the availability of pure growth hormone from recombinant DNA synthesis, the causes and effects of hormone heterogeneity may be studied more easily in the future.

Evolution and the Definition of a Hormone

Prior Findings

In classical terms, hormones are substances produced by specific cell types in an endocrine gland. These cell products are released from the endocrine gland into the bloodstream and transported to a distant site, where they exert a specific effect on other body cells or tissues or organs. Each hormonal peptide was traditionally considered a unique product of a single cell type.

Research by intramural scientists and grantees now has shown that these conventional boundaries may be too limited. The particular type of cell that produces some hormones has been found outside of endocrine glands. In addition, it has been found that cancers from nonendocrine tissues and diverse neurons can produce peptide hormones. Recently, it has been demonstrated that other cell types (nonneural and nonmalignant) can synthesize certain peptide hormones. Insulin has been detected in the brain, the peripheral nerves, and in cultured cells of diverse origin. ACTH (adrenocorticotrophic hormone) has been found not only in its conventional site—the pituitary gland—but also in the brain, the placenta, and other tissues.

The diversity of cell types producing hormones and hormone-like substances is not limited to human and other mammals, and in fact, findings in other species have produced fascinating evidence for the continuity of living organisms and new insight on the basic nature of hormones as forms of intercellular communication.

The endocrine systems most studied are those in vertebrates, although endocrine systems exist in insects and other invertebrates and in plants (e.g., auxins). Recently, hormonal peptides found in vertebrates have been reported in various invertebrates, and evidence is now presented that some peptide hormones are found in unicellular organisms (such as bacteria) as well. In addition, receptor and effector pathways for hormone-type action have been found in these organisms. The concept thus emerged that hormones probably developed early in unicellular organisms as a means of intercellular communication.

Theories have been developed about the evolution of the vertebrate nervous and endocrine systems that suggest that the nervous system is the older of the two phylogenetically. The results of recent experiments imply that intercellular communication by chemical mechanisms arose very early in evolution and that many of these chemical messengers have remained largely unchanged. Furthermore, as organisms became more complex, some cells and tissues specialized to produce chemical messengers, while others specialized as receptors of the message. Since both the nervous system and the endocrine system use chemical messengers, they could have evolved independently and simultaneously. Concurrent evolution may explain the overlap between the endocrine and nervous systems that has been observed for many years. This theory also helps explain why hormones may be produced by tumor tissues or by cells not associated with the endocrine organ.

Recent Advances

Institute researchers grew unicellular organisms in synthetic media made up of simple ingredients. The organisms were then subjected to extraction procedures, and peptides similar to the mammalian hormones insulin, ACTH, and somatostatin were detected by radioimmunoassay. These materials were purified and tested and shown to have biological activity. Controls and safeguards were developed to assure that there was no contamination of the extracts from outside sources. Organisms tested included protozoa, fungi, and the bacterium *E. coli.*

Several vertebrate hormones are known to have biological effects in unicellular organisms, and at least two mammalian hormones are known to have specific receptors in unicellular organisms. As an example, the amoeba (*Amoeba proteus*) has receptors for opiate-like peptides, which have an effect (inhibiting pinocytosis, or direct engulfing of liquid) that is reversed by naloxone, a narcotic antagonist specifically blocking opiate receptors.

Research Directions

Studies are in progress to discover other peptide hormones in unicellular organisms, as well as hormone receptors. Genetic studies showing that unicellular organisms have genes for peptide hormones are also in progress.

Evidence is needed to define the role played by these hormones and receptors in the biology of the organism and to document further the presence of integrated hormonal systems (hormonal source, receptor, and effector) at the one-cell stage. Most important, the larger context of research on the molecular basis of intercellular communication should be pursued, encompassing as it does the functioning of the nervous and endocrine systems and a wide range of local (paracrine) systems for cellular effects on one another.

Metabolic Diseases

Cystic Fibrosis: Decrease in Chloride Reabsorption

Prior Findings

Cystic fibrosis, the most common lethal genetic disease of Caucasian populations, appears to be an inborn error of metabolism involving all exocrine glands (those excreting via a duct to an internal or external body surface, as the sweat glands and salivary glands do) and, most likely, other tissues and organs. This characteristic generalized dysfunction of the exocrine glands results in a clinical picture of recurrent pulmonary disease, pancreatic insufficiency with malabsorption of nutrients, and elevated sweat electrolyte concentrations. Numerous other organs are also affected in a primary or secondary fashion. The key to improved survival appears to be early diagnosis and aggressive antibiotic therapy; approximately 90 percent of deaths from CF are attributable to pulmonary disease. Many patients are surviving now into adulthood, whereas as recently as two decades ago, the disease was almost uniformly fatal in early childhood.

Investigations conducted and supported by the NIADDK and other NIH Institutes are aimed specifically at defining the cause and physiological effects of cystic fibrosis and its associated biochemical aberrations and at improvement of methods for prompt diagnosis, more effective treatment, recognition of carriers for the disease, and eventual prevention of the disorder.

Abnormal electrolyte transport appears to be a primary characteristic of CF; however, a full description of the transport anomaly in the various affected tissues has not been achieved, nor has an elucidation of the mechanism responsible for the anomaly.

Because the sweat of CF patients has long been known to contain higher than normal concentrations of electrolytes, a number of investigators have focused on possible altered mechanisms of ion transport in exocrine glands and epithelia as an expression of the CF defect. Since studies of active sodium-potassium transport mechanisms in CF patients have shown no apparent defect, attention has turned to studies of passive transport channels. Thus, one group found abnormally large negative electrical potential on the luminal side of CF lung mucosa and interpreted this finding to indicate an abnormally high rate of cation (e.g., sodium) permeability into CF tissue.

Recent studies indicate that CF may involve a defect in the reabsorption of sodium in sweat, salivary, and pancreatic ducts. In sweat and salivary ducts sodium reabsorption appears to be decreased in CF patients, while it may be enhanced in pancreatic ducts and respiratory mucosa. Altered ion transport in CF may cause a quantitative difference rather than a qualitative one. A recent study of perfused sweat gland ducts showed that, at very slow perfusion rates, sodium content of the sweat emerging from the duct is the same for normal and CF tissue, thus indicating that the transport defect may be one affecting rate rather than consisting of an absolute blockage of ionic flow.

NIADDK-supported research on the electrolyte transport defect in the sweat glands and other tissues of cystic fibrosis patients could lead to more effective treatment of this inborn error of metabolism.

Recent Advances

An alternative explanation of the transport defect, proposed by an NIADDK-supported group, is that it involves the negatively charged chloride anion permeability rather than cation (positive ion) permeability. This group studied the sweat glands of normal and CF subjects, rather than respiratory mucosa, and replicated the basic finding of the earlier work: abnormally large negative electrical potentials on the interior (luminal) side of CF glandular linings (epithelia); however, the group pointed out that this result could be caused by either increased sodium permeability or decreased chloride permeability. Additional data, collected both from patients and in the test tube, clearly supported the presence of a reduced chloride permeability in CF sweat duct epithelia. Identification of the defect as one involving chloride permeability could lead to more effective treatment of CF patients (i.e., control of the transport defect resulting in better management of electrolyte balances).

Research Directions

Additional studies of electrolyte transport phenomena should be conducted in the sweat gland

and respiratory tract to seek a common mechanism explaining the transport behavior of epithelia in this disease. Comparable studies of epithelia in the pancreatic duct and intestinal mucosa should also be pursued by investigators to relate these affected tissues to respiratory and sweat duct results. The role of electrolyte transport in both secretory and reabsorption processes should be investigated.

Maple Syrup Urine Disease (MSUD): A Method for Identifying Carriers

Prior Findings

In this disease, defective functioning or deficiency of an enzyme necessary to break down the amino acids leucine and isoleucine (into their ketoacid derivatives), in metabolic processing of proteins in food, gives the urine a characteristic odor like maple syrup. A third amino acid (valine) is affected as well; all three have branched molecular structures, accounting for the alternate name of this inherited metabolic disorder, branched-chain ketoaciduria. The enzyme is called a branched-chain ketoacid dehydrogenase (BCKA dehydrogenase). The affected infant may be normal at birth, but soon develops signs of the disease, leading to mental retardation and retarded motor development. If the diagnosis is not made promptly and dietary restriction begun, most of these children will die in the first month. If treatment is begun before about 10 days of age, normal growth and development can be achieved.

Those who have the mutant gene from both parents (homozygotes) will develop the disease; those who inherit it from only one parent (heterozygotes) are carriers of the disease. Unfortunately, carriers of the mutant gene, whose children could be afflicted with the disease, could not previously be identified, and thus, genetic counseling (to avoid pregnancies that could result in homozygous infants with the clinical disease) has not been possible.

Recent Advances

Work under NIADDK support has resulted in the development of an assay for BCKA dehydrogenase in disrupted cultured fibroblasts (connective tissue cells), which can differentiate between normals, (obligatory) heterozygote carriers, and afflicted homozygotes. While the disrupted cells of normals showed a well-defined uniform rate of activity for BCKA dehydrogenase, disrupted cells from carriers showed a clear dual rate of activity dependent on the concentration of the accumulating intermediate metabolite. This dual activity profile seemed to be related to the expression of both the normal and the mutant gene in the carrier. Afflicted homozygotes showed lack of BCKA dehydrogenase activity in the developed assay.

Research Directions

The availability of this assay could result in a broad-scale prevention of this devastating disease. The assay is being validated on a small population group of Pennsylvania Dutch with a high rate of intragroup marriages, in which an increased rate of MSUD would be expected.

Lysosomal Storage Diseases

Prior Findings

There are about three dozen disorders (including well-known entities such as Tay-Sachs disease and Hurler's syndrome) in which an enzyme deficiency causes the accumulation of lipid or carbohydrate material in specialized cellular bodies, the lysosomes. Because enzymes can be taken up from the exterior of the cell and transported into lysosomes, enzyme replacement had been proposed two decades ago as a way to treat such disorders. However, many attempts have been unsuccessful because the difficulties of enzyme replacement had been greatly underestimated.

Recent Advances

Work of the past year or two has shown that the process of transport from the cell exterior to lysosomes is complex and involves recognition of a specific signal on the enzymes by receptors on the surface of the cell. Several organelles participate in the process, some of which have properties (such as an acidic environment) previously thought to be unique to lysosomes. Likewise, the process by which cells normally make and transport their own endogenous enzymes to lysosomes is a complicated one, involving a number of modifications of the structure of the enzymes as they pass through different portions of the cell on the way to lysosomes. Genetically transmitted errors may occur at any stage of this process. The most dramatic example occurs in I-cell disease (mucolipidosis II), in which failure to make the specific signal that targets newly made enzymes to lysosomes causes these enzymes to be misdirected and secreted outside the cell. Analogous mutants obtained in cultures of nonhuman cells serve as useful models for genetic diseases of lysosomal enzymes.

Research Directions

Grafts of normal tissue have been proposed as a practical means of enzyme replacement. Intramural and extramural scientists have collaborated in identifying a canine model for Hurler's syndrome that will be used to study the value of bone marrow transplantation. Intramural NIADDK and NICHD scientists are collaborating to assess the value of amniotic membrane transplantation for treatment of mucopolysaccharide

storage disorders. The cloning of genes for lysosomal enzymes, undertaken in many institutions including NIADDK intramural programs, will extend our understanding of the diseases to the level of the actual mutation and may eventually solve the problem of enzyme supply for therapeutic purposes.

The Nature of the Inborn Defect in Cystinosis

Prior Findings

Children in the first or second year of life who develop signs of renal disease, perhaps with bone disease (rickets) and thyroid and retinal damage, may have the inborn defect known as cystinosis, in which large amounts of the amino acid cystine collect in cellular lysosomes (small bodies storing enzymes inside the cell) throughout the body. Cystinosis is a recessive disorder (expressed only when the defect is inherited from both parental lines) and usually causes death from renal failure by the end of the first decade, if untreated.

Research on the disease led to an experimental (test-tube) method for loading large amounts of cystine into normal cultivated lysosomes, which, in turn, led to an increased understanding of the ways by which normal cells dispose of excess cystine.

Recent Advances

Studies showed that cystine is rapidly lost by the lysosomes of intact, normal cells, but is not lost by the lysosomes of intact, cystinotic cells. Thus, cystine-loaded normal lysosomes from human lymphoblasts showed that efflux of cystine was greatly facilitated by adding adenosine triphosphate. In contrast, cystine efflux from lysosomes of cystinotic individuals was unresponsive to ATP. Additional studies indicated that defective ATP-dependent transport of hydrogen ions across the membrane (a defective membrane proton pump) is responsible for the accumulation of cystine in lysosomes of cystinotic children.

Research Directions

Identification of the defect in cystinosis will allow researchers to concentrate their efforts on studies of the faulty transport system and will, therefore, accelerate finding effective cures for the disease. To develop effective treatment modalities, detailed studies are needed on the proton-pump ATPase enzyme system in normal and cystinotic cell cultures. Such studies will allow comparison of the two systems and identification of the components responsible for the defect in the membrane transport system.

Activation of a Defective Enzyme to Treat an Inborn Error

Prior Findings

The mucopolysaccharidoses are but a few of the disorders known collectively as inherited diseases of connective tissue. The common feature of this entire group is that some element of connective tissue (collagen, elastin, mucopolysaccharide) is altered due to an apparent inborn error of metabolism and growth. This is an area receiving concentrated attention by NIADDK intramural scientists.

Mucopolysaccharidosis VI (MPS VI) is an inborn error of metabolism due to deficiency of the active enzyme arylsulfatase B (ASB). In recent studies, a feline model for the study of MPS VI was identified. The reduced ASB enzyme activity present in the diseased cat allows dermatan sulfate, formed in the normal metabolic process, to accumulate in tissues and body fluids, causing multiple bone and facial deformities and corneal opacity. Until recently, there was no successful method available for clearing the accumulated dermatan sulfate from diseased subjects.

Recent Advances

A means of correcting or reactivating defective enzymes through oral or intravenous administration of various chemical agents recently has been developed. The two subunits of the normal enzyme of cats are bound together, while in the mutant enzyme, they are separate and inactive. Chemical manipulations by means of cysteamine (beta-mercaptoethylamine, a part of one of the body's coenzymes) reunited the two subunits and activated the mutant enzyme. Intravenous infusion of cysteamine in MPS VI cats partially reestablished the ASB activity by chemically modifying a sulfur-containing group in the enzyme. As a consequence of ASB activation in the MPS VI cats, accumulated dermatan sulfate was cleared and reduced to about half the preinfusion level for the duration of the study.

These studies provide a model for the treatment of inborn errors of metabolism in man by increasing a mutant enzyme's residual activity. This approach may be useful in the design of therapeutic modalities in a variety of human genetic diseases involving defective enzymes.

Research Directions

Such research results suggest strategies for the targeted delivery of therapeutic agents to specific disease sites and the possibility of reactivation of other mutant enzymes, in clinical medical use.

Since cysteamine has been used safely in the treatment of cystinosis in humans, the possibility of extending the feline studies to humans will be explored. On

the other hand, in preliminary studies, a derivative of cysteamine, cystamine, also showed enzyme activity enhancement in the cat. This compound is tasteless and palatable, allowing oral administration instead of infusion. Studies are planned to assess the value of this derivative as a potential drug of choice in the treatment of MPS VI.

Obesity and Resistance to Insulin

Prior Findings

Insulin binding to cell receptors is known to be reduced in obesity, and fasting levels of insulin are elevated in obese people. An insulin-mediated decrease in affinity for binding sites appeared to contribute to resistance to insulin itself. Because insulin binding also can be affected by exercise, steroid hormones, diet, and the acid-base balance, it has been of interest to learn which factors are involved in the decreased binding seen in obese individuals.

Recent Advances

Institute investigators working with (nondiabetic) Pima Indians have compared the binding of insulin by fresh monocytes (white blood cells), still subject to nutrient and hormonal influences from the donor's blood, with the binding shown by fibroblasts (connective tissue cells) being maintained in tissue culture to eliminate the effect of nutrient and hormonal influences unique to the donor. Both types of cells were from donors with varying degrees of obesity. The results showed that variations in insulin binding in both types of cells correlated with the obesity of the cell source, suggesting that insulin resistance in obesity may in part reflect inherent (genetic) differences at the site of the insulin receptor.

Research Directions

Comparisons must now be made of lean and obese individuals to see if inherent cellular differences in insulin binding can be demonstrated. The relationship of these findings to the earlier demonstration that a low calorie diet can improve insulin binding in obesity should be explored. Further studies are needed to see if obese individuals who return to normal weight and are eating a normal diet have normal insulin receptors and normal insulin sensitivity. Finally, a full understanding of the changes measured in insulin binding requires further clarification of the molecular events associated with the insulin-receptor interaction.

Special Programs

Diabetes Centers

Both Diabetes Research and Training Centers (DRTC's) and Diabetes-Endocrinology Research Centers (DERC's) are required to have a strong base of high-quality, ongoing biomedical research. The center grants provide for core facilities (shared resources), pilot and feasibility studies, and program enrichment.

While biomedical research is the singular focus in each of the four DERC's, the seven DRTC's also include training of medical and allied health professionals, continuing education, and model demonstration and outreach activities. Limited funding is available in the DRTC's for research related to training and information transfer. The current-year activities and accomplishments of the DRTC program are described in detail in chapter VI.

Diabetes Data Group

Concerns of the National Diabetes Data Group include defining diabetes-related data needs, coordinating the collection of data from multiple sources, standardizing collection procedures and terminology, making reliable data available to users, and measuring the medical and socioeconomic impact of diabetes. The data group, which was authorized by Congress in 1980, consists of epidemiologists, representatives of Federal and voluntary-sector organizations, and experts in the research, nutritional, and socioeconomic aspects of diabetes. It is the data group's mission to establish, in concert with the National Diabetes Information Clearinghouse, "a system for the collection, storage, analysis, retrieval, and dissemination of data concerning diabetes, including, where possible, data involving general populations for the purpose of detecting individuals with a risk of developing diabetes." Through its data collection and analysis activities, the data group serves as a central source for the accurate statistics that are essential to rational development of scientific priorities and public health program plans.

The data group also promotes opportunities for new research on epidemiologic and public health aspects of diabetes by advising grant applicants regarding the suitability and feasibility of proposed epidemiologic research and by serving as a consultant to the NIH Division of Research Grants and to the staff of the Division of Diabetes, Endocrinology, and Metabolic Diseases. The data group provides national data to researchers to contrast with their community-based epidemiologic data and was instrumental in forming a council on epidemiology within the American Diabetes Association in order to stimulate epidemiologic research through that body.

National Diabetes Information Clearinghouse

The National Diabetes Information Clearinghouse (NDIC) is the central point for the collection and dissemination of information about education and

scientific materials, programs, and resources relevant to diabetes. Over 9,000 health care providers requested that their names be placed on the NDIC mailing list so that they can receive the information it provides on a regular basis. Over 4,000 pieces of diabetes educational materials that are widely available for purchase or at no cost have been identified and abstracted. Currently, about 3,500 abstracts are included in an automated data system. Because health care providers often need information about a variety of health conditions, the director of the NDIC has taken the lead in developing a cooperative health information data system. The Centers for Disease Control and other information dissemination programs at the NIH have enthusiastically joined forces with the NDIC, and this new system is becoming a reality.

Answering requests for information is a continuing NDIC activity. The NDIC receives over 800 letters and telephone calls a month asking for information about every aspect of diabetes and self-care practices. An evaluation of the NDIC's major products, the annotated bibliographies, was conducted through a random sample of users. The results of the evaluation demonstrated that the bibliographies are highly regarded in terms of usefulness and quality. Each user shares each bibliography with an average of six additional people. An extrapolation of the data suggests that between 45,000 to 92,000 publications have been ordered by the users as a direct result of receiving these bibliographies.

The clearinghouse not only provides information but also identifies areas needing additional educational materials and assists in developing such materials. The clearinghouse is committed to increasing community awareness and understanding of diabetes as a health problem and to encouraging effective patient, family, and community educational programs.

National Hormone and Pituitary Program

In 1963, with support from the College of American Pathologists, the NIADDK instituted the National Pituitary Agency, now known as the National Hormone and Pituitary Program. Since then, the program has provided supplies of hGH for research related to treatment of hypopituitary dwarfism and other growth disorders. This work helps, each year, about 2,000 children with hypopituitary dwarfism to achieve more normal growth, as part of 234 clinical projects that received hGH for research and treatment purposes. With research advances over the years, it was found that other anterior pituitary hormones could be extracted from the same glands, and the scope of the program was therefore expanded to provide for the distribution of follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, prolactin, adrenocorticotropic hormone, and lipotropin.

Support by the NIH has allowed expansion of the program to include distribution of hormones and antisera for immunochemical research projects; about 10,000 projects were supplied with approximately 25,000 vials of standardized hormones and antisera. For human studies, 10 different hormones and their antisera were provided. Similar materials specific for rat, ovine, bovine, and porcine experiments were supplied.

The NHPP also illustrates the impact of advances in endocrinology research on clinical medicine. Already, hGH has been synthesized, by recombinant DNA methods, in bacteria. A pure and effective synthetic hGH preparation can be expected to supplement and eventually displace the extraction of hGH from pituitary glands. As yet, no comparable accomplishment has been possible for the complex glycoprotein structures of the gonadotropins of the pituitary and placenta, and these tissues remain the only available source. The availability of these rare substances, through the activities of the NIADDK's distribution program, has proven invaluable in many extensive programs of basic and clinical investigation.

Program Accomplishments

The Division director has established a program advisory committee, both to review recommended planning initiatives and to develop, refine, and prioritize long-term programmatic objectives. Membership on this committee includes senior representatives from the Division of Intramural Research as well as various other authorities in diabetes, endocrinology, and metabolic diseases from the extramural research community.

During the past year, the Division director has also coordinated a major new cooperative initiative between the Department of Health and Human Services and the American Diabetes Association in the area of disease prevention and health promotion. In addition, he and other members of the staff have worked closely with representatives of the Pew Foundation to help ensure continuity of support for the National Diabetes Research Interchange, a private organization established in 1981 under the auspices of the Juvenile Diabetes Foundation to expand the availability of human tissues and organs for research purposes. During the past year, particular emphasis has been given to completing the initial planning phase of the Diabetes Control and Complications Trial and implementing the trial's phase II feasibility study. The director has worked closely with representatives of the Endocrine Society and various NIH Institutes in assessing progress to date in responding to the recommendations of the Task Force to Evaluate Research Needs in Endocrinology and Metabolic Diseases. An update and status report on progress since 1979 was prepared for the Senate Committee on Appropriations.

Request for Applications Is Issued on Immunologic Mechanisms in the Development of Diabetes

An announcement was issued requesting research grant applications in the area of the immunopathogenesis of diabetes. The NIH sponsors broad-based programs of basic and clinical research into the cause, cure, and prevention of diabetes and its complications. Recent evidence for an altered immune response in the development of IDDM has prompted this solicitation in an effort to stimulate additional research in the area of immunopathogenesis of diabetes.

This NIADDK request for applications, cosponsored with the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases, is prompted by a perceived need to elucidate the immunopathogenetic mechanisms important in the development of IDDM and to obtain new basic information from population studies that relate these various factors to the incidence and prevalence of the disease and the development of its complications.

A recent workshop sponsored by the NIADDK, the National Institute of Allergy and Infectious Diseases, and the National Institute of Dental Research reviewed the available data in the areas of population and family studies, identical or fraternal twin studies, the relationship between IDDM and virus infection and other autoimmune diseases, lymphocyte invasion of the pancreas, detection of islet cell antibodies and islet cell surface antibodies, association of histocompatibility (HLA) types with IDDM susceptibility, and successful intervention in the immune suppression in diabetic animal models. Assessment of the available data provided the basis for workshop participants to make recommendations on the need for future research in the areas of epidemiology, etiology, and pathogenesis of diabetes as they relate to the immune system.

It is hoped that this request for applications will stimulate research in these areas, particularly by encouraging investigators with a background in immunology to study the mechanisms of immunopathogenesis associated with IDDM.

Interagency Conference Introducing a New Guide for Physicians on Prevention and Care of Diabetic Complications

One of the major accomplishments of the Diabetes Mellitus Interagency Coordinating Committee (DMICC) during the past year was a conference to introduce a National Diabetes Advisory Board-sponsored publication, *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*, to a selected group of individuals in the Federal sector concerned with primary care of diabetic patients.

The conference was held on February 25-26, 1983, at the Uniformed Services University of the Health Sciences. It was evident from preliminary plans developed at the conference that each agency has unique needs and opportunities. The three major Federal agencies with responsibility for direct provision of health care services include the Veterans Administration, the Department of Defense, and the Health Resources and Services Administration. As a result of this conference, the participants from the three agencies formulated a plan for dissemination and use of the *Guide* in their agencies.

Further dissemination of this *Guide* is being undertaken under the aegis of the National Diabetes Advisory Board. An effort is being made to make diabetologists aware of its existence, since they will be the group being asked for advice and receiving referrals, before its wide dissemination to primary care practitioners. The dissemination in both private and Federal sectors will be followed closely, and some evaluation of the impact of the *Guide* on care of diabetic patients will be made.

In general, the recommendations can be implemented in physicians' offices and other outpatient settings. Specifically, the conference provided an excellent example of the benefit of interagency collaboration to transfer effectively new knowledge to the practice and delivery of health care in the area of prevention and treatment of diabetes-related complications.

Contracts for Research Resources in Diabetes

A contract was negotiated for the maintenance and distribution of spontaneously diabetic (and control) BB Wistar rats. This model has been particularly useful to the diabetes research community because it has characteristics similar to those found in human IDDM.

A noncompetitive proposal was issued for the support of the National Diabetes Research Interchange (NDRI). This centralized tissue resource has provided human material to investigators for research that would not otherwise be possible. It is anticipated that this contract will be negotiated in the fall of 1983.

Workshop on Immunosuppression in Diabetes

A workshop was convened by the Institute to assess the state of the art of the proposed use of immunosuppression to possibly modify, prevent, or even cure the diabetes syndrome. Approximately 20 NIH scientists attended the meeting. The area is still controversial,

with some scientists advocating cautious human trials and others recommending suspension of human trials until further research has proven that benefits outweigh risks. All agreed that immunotherapy in IDDM is regarded as an *experimental procedure*. Workshop participants also concluded that development of more specific guidelines for this area of experimental clinical management must await the demonstration of a more definitive risk/benefit ratio than has so far been exhibited by the preliminary data currently available. It was further recommended that these concerns and the preliminary nature of any available results should be conveyed to practicing physicians and to concerned parents in order to forestall any widespread attempts at immunosuppression in IDDM patients, particularly children, until more information is available. It was reiterated that any attempt at immunomodulation of diabetic patients by other than major centers with a sufficient number of patients to allow randomized, controlled trials and using the most modern techniques to assess B-cell function and to monitor closely a large number of immunologic parameters is contraindicated.

Jointly Sponsored Conferences on Diabetes

The program supported three conferences in conjunction with the American Diabetes Association, the Juvenile Diabetes Foundation, and the Scientific Committee of the Second International Symposium on Insulin Receptors on the topics of lessons from animal diabetes, mechanisms of beta-cell injury, and the insulin receptor.

Accomplishments of the National Diabetes Data Group

The data group has embarked on three major projects:

(1) Achievement of an international consensus on methodology for measurement of glycosylated proteins and their use in clinical practice, research, and screening for diabetes. On May 12-13, 1983, an international workshop was held in Bethesda to discuss the problems in methodologies for laboratory measurement of glycosylated proteins, to propose procedures for calibrating such methods from laboratory to laboratory, and for developing an international reference standard. An expert committee was formed to develop recommendations for appropriate NIH actions to address these issues.

(2) Assessment of the economic methodologies for measuring cost of disease and generation of accurate data on the economic impact of diabetes and its complications. A workshop was held with officials from the National Center for Health Statistics (NCHS) and the National Center for Health Services Research (NCHSR) to discuss the various current methodologies for assessment of the cost of illness. Several promising new methodologies are being developed, but these have not been tested thoroughly. Consequently, a consensus was reached that the data group should employ the method most commonly used to date, namely the human capital approach. The NCHS and the NCHSR are collaborating with the data group in developing more accurate data on direct costs of medical care for diabetic patients.

(3) Development of a major revision and update of the 1977 data compilation on diabetes, to respond to the data needs of researchers, public health officials, clinicians, and other persons and agencies concerned with diabetes. In this project, the data group continues to work in close collaboration with NCHS in assessing the national data on diabetes collected by that agency. With the Division of Health Examination Statistics, the data group has analyzed oral glucose tolerance tests on a statistical sample of the U.S. population to develop norms and standards for plasma glucose levels and to determine the prevalence of undiagnosed diabetes and impaired glucose tolerance. This Division is also conducting a study of Hispanic-Americans, for which the data group developed the medical history and household questionnaire and the clinical and laboratory tests to be used. The Divisions of Analysis, Mortality Statistics, and Health Care Statistics are participating in development of the comprehensive data book, by supplying NCHS data on multiple causes of death among people with diabetes, sociodemographic characteristics of people with diabetes, and medical care aspects, including ambulatory, hospital, and nursing home care.

Support for Production and Distribution of Hormones

A contract was negotiated with the Research and Educational Institute, Inc., at Harbor-UCLA Medical Center, for the production of rat and ovine pituitary hormones. These hormones will be distributed through the Institute's Hormone Distribution Program to investigators both in this country and abroad.

The Hormone Distribution Program continues to collaborate with the National Institute of Child Health and Human Development and with the U.S. Department of Agriculture on the distribution of hormones and antisera for research in the United States and in foreign countries.

Conference on Growth Hormone

A conference grant was funded to the University of Maryland (Principal Investigator, Dr. Salvatore Raiti) for a November 1983 conference on growth hormone, in Baltimore, Maryland.

Assessment of Research Support for Metabolic Diseases

Recent legislative developments and public awareness of the problems associated with rare diseases (mainly lack of available treatment modalities) have led the NIH to evaluate its research support for rare diseases. The Metabolic Diseases Program staff concentrated its efforts toward facilitating inter-Institute communication in the areas relating to research support of inherited metabolic disorders and broadening the science base by facilitating international collaborations. Program staff initiated the formation of an Ad-hoc NIH Workgroup on Inherited Metabolic Disorders, with the purpose of planning to assess NIH support of research and to reevaluate research needs in this area of biomedical science.

Workshop to Broaden the Research Base for the Study of Inborn Errors of Metabolism

Responding to requests from the scientific community and officers of the Society for Inherited Metabolic Disorders, the program organized and cosponsored, in conjunction with four other Institutes, the U.S.-Japan Workshop on Research in Inborn Errors of Metabolism held on March 19-20, 1983, at the NIH. Interested United States' and Japanese scientists participating in the workshop established the U.S.-Japan Committee for Research in Inborn Errors of Metabolism. The committee will serve as a facilitator for international activities in order to foster communication through exchange of scientific information, exchange of data bases on active research programs and investigators, and the exploration of governmental programs of mutual interest and relevance to inborn errors of metabolism; exchange of research materials (e.g., cell lines, drugs, clinical trial protocols, gene frequency data, animal models, dietary control data, etc.); and short-term exchange of research scientists.

Conferences

Conferences on research and clinical developments and advances in biomedicine facilitate the immediate exchange of information and cross-fertilization among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions. It is the fastest and most effective type of cross-fertilization process in biomedical research.

The Institute sponsored or supported the following conferences during the last fiscal year.

Conference on Cystic Fibrosis Heterozygote Detection and Prenatal Diagnosis. New York, New York, March 30-April 2, 1982.

Colloquium on Advances on Diabetes Epidemiology. Paris, France, May 3-7, 1982.

Diabetes Mellitus and Renal Disease. Arlington, Virginia, October 15-16, 1982.

Effects of Hormones on Intracellular Membrane Systems. Woudschoten, The Netherlands, May 1983.

Symposium on Pituitary Tumors. Boston, Massachusetts, June 5-8, 1983.

VIIIth American Peptide Symposium: Chemistry and Biology of Peptides. Tucson, Arizona, May 22-27, 1983.

Gordon Research Conference on Hormone Action. Meriden, New Hampshire, August 7-12, 1983.

VIIIth International Conference on Calcium Regulating Hormones. Kobe, Japan, October 16-21, 1983.

Symposium on the Regulation of Cell Function by Protein Phosphorylation. East-sound, Washington, June 10-11, 1983.

Gordon Research Conference on Lipid Metabolism. Meriden, New Hampshire, June 20-24, 1983.

Fourth International Symposium on Calcium Binding Proteins. Trieste, Italy, May 16-19, 1983.

Gordon Research Conference on Protein. New Hampton, New Hampshire, June 27-July 1, 1983.

Program Plans

Diabetes Control and Complications Trial: Phase II Begins

The Diabetes Control and Complications Trial (DCCT) has been organized by NIH to answer this important question: Does normalizing blood glucose help to prevent or ameliorate diabetic complications? This largest, prospective randomized study of this problem ever undertaken will comprise 21 centers throughout the United States and Canada and will proceed in three phases: a planning phase, a 2-year feasibility trial, and the full-scale study, which will include about 1,000 patients over an 8- to 10-year period.

Controversy regarding whether or not IDDM should be managed by aggressive treatment methods that attempt to achieve normalization of blood glucose levels has existed for over 50 years. The need for a carefully controlled study to resolve this controversy has been documented in the scientific literature and in the reports of several advisory groups for many years. In the past 5 years, new ways to treat IDDM have been developed, and the application of these new techniques now enables this question to be rigorously tested. It is not known whether these new techniques, which allow near-normalization of blood glucose, are any better than standard management in preventing or

ameliorating the serious complications of IDDM, which can include stroke, blindness, heart disease, kidney failure, gangrene, and nerve damage. Treatment method has been the single most important and controversial clinical question in diabetes; the answer will affect how diabetes is managed in the future.

The Institute formulated plans for the study in fiscal year 1981 and implemented them in 1982. The study will be conducted in four phases, as described below.

Phase I of the four sequential phases of the DCCT was initiated in February 1982 and completed in February 1983. The objective of phase I was to develop a protocol for a 2-year study to assess the feasibility of conducting a full-scale, long-term clinical trial to determine the relationship of metabolic control to the clinical course of early vascular complications of IDDM.

Twenty-one clinical centers were funded in fiscal year 1982 with research cooperative agreement grants; the data coordinating center was funded by contract.

In January 1983, the DCCT Policy Advisory Group (PAG) and the DCCT Data, Safety, and Quality Review Group (DSQ) independently reviewed and approved the revised draft protocol and recommended that the study proceed into phase II. The PAG and the DSQ are independent advisory groups, who are not in any way involved in the conduct of the study, with expertise in all scientific and technical areas relevant to the clinical trial. The PAG is charged with providing advice on the overall policy and direction of the trial. The charge to the DSQ is to oversee all aspects of study operation to ensure data quality and the safety and well-being of volunteer participants.

Phase II will be a 2-year, multicenter, randomized, controlled study of 252 volunteers to determine: (1) whether patients can be recruited who fulfill the eligibility criteria and who are willing to be randomized to either a standard or an experimental therapy; (2) whether a clinically and statistically significant difference in the level of blood glucose control can be maintained between the two groups over a 2-year period; (3) the safety, efficacy, and acceptability of the two treatment regimens; and (4) whether biochemical and clinical outcomes can be measured and documented with acceptable precision.

If these goals are met, it is anticipated that the DCCT will proceed to the long-term study of the impact of the two therapeutic strategies on the complications of IDDM using an expanded patient population. This decision will be based on advice provided to the NIADDK Director by the PAG and the DSQ. Each of these oversight groups will assess independently the results of the feasibility study (phase II) to determine whether the goals have been met and the desirability of proceeding with phase III.

All required central laboratories, reading and coding centers, and other support units necessary for conduct of phase II were identified during the past year. In addition, a detailed manual of operations and appropriate data forms for phase II were developed and finalized. Standards for clinic certification were also developed and implemented.

The primary complication to be assessed in the full trial (phase III) is diabetic retinopathy, and two categories of patients will be recruited: those with no evidence of retinopathy and others with early signs of this complication. This study will make it possible to determine simultaneously whether tight blood glucose control can prevent the development of eye complications and whether tight control can halt or reverse eye damage at an early stage. Study participants will be followed carefully to determine if one method of management is superior to the other in preventing, delaying, reversing, or alleviating the early vascular complications of diabetes.

Phase IV, analysis and reporting of data generated in the trial, will conclude the study. The information learned from the clinical trial will be published in the medical literature to assist physicians in choosing the best treatment for their diabetic patients.

The conduct of the DCCT illustrates the process of cooperation among NIH Institutes, three of which are contributing funds or technical support to the project to supplement NIADDK efforts with respect to prevention of cardiovascular, neurological, and eye complications.

In addition, the Division of Research Resources (DRR) has actively promoted the DCCT among the directors of the General Clinical Research Centers (GCRC). Seventeen of the 21 participating DCCT centers have GCRC's and the DRR has encouraged the directors to facilitate use of these centers by the DCCT investigators. The private sector is participating, as well; various commercial organizations have donated supplies, equipment, and services. These contributions represent considerable and most welcome support.

Diabetes Workshop for Medical Students

The need for physicians electing to pursue careers in diabetes research has never been more acute. The remarkable progress made in the Diabetes Research Program in the past several years has created new and expanding opportunities for clinically trained investigators. These opportunities, unfortunately, are appearing at a time when the proportion of physician-investigators is declining. The Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel noted in their report to the National Academy of Sciences (1981) that the number of M.D.'s in NIH research training programs has not changed appreciably since 1976 and is currently well below an appropriate level. The committee urged throughout the report that a great effort be made to

address this problem. In addition, the NDAB in all four of its reports to Congress (1979-1982) has noted the severe shortage of physicians engaged in diabetes research.

Although the physician enters research training most commonly at the end of the last year of the residency program, many points along the continuum of medical education offer the opportunity to influence the physician's decision to embark on a research career.

In January 1982, the Juvenile Diabetes Foundation (JDF) sponsored a workshop for medical students to introduce them to current research in diabetes. Seventy-seven students from as many medical schools attended the 2-day workshop hosted by the University of Chicago DRTC. Response from attendees was extremely positive, and the JDF intends to repeat the meeting annually. The 1983 workshop was held at the DRTC at Washington University in St. Louis with an enrollment of over 100 medical students. Funding to support these workshops has been obtained from many sources, including an annual contribution from the NIADDK through the NDIC.

The Training of Clinicians in Epidemiological Methods for Diabetes

Epidemiology is the study of the patterns of disease occurrence and therefore deals with the causes (etiology) and development (pathogenesis) of disease.

Epidemiologic research on the etiology and pathogenesis of diabetes and its complications is needed to complement clinical and basic research studies. Such research is necessary to translate clinical and laboratory findings on diabetes into community control programs, to develop etiologic hypotheses from human population studies that can be further investigated in the laboratory, to validate clinical impressions in unselected human populations, to determine the natural history of the various types of diabetes, and to evaluate clinical management and therapeutic interventions. The problem is the dearth of persons trained in diabetes epidemiologic research methods, both in the United States and internationally. In the main, clinical diabetes researchers have received virtually no training in epidemiologic methods and biostatistical analyses, thus leading frequently to biased and inaccurate research results due to such factors as improper selection of patients and controls, inadequate sample sizes, or lack of matching or confounding factors. A training seminar is planned to provide an intensive short course in epidemiologic statistical methods appropriate to research on diabetes and its complications.

The seminar would be limited to 40 students, selected competitively by an NIADDK review committee, and 10 persons invited by the NIADDK to participate as full-time faculty. It would last for 10 working days and would consist of plenary lectures and small group sessions under the supervision of the faculty. Among the subjects to be included are the basic methods of clinical epidemiology and biostatistical analysis, research design incorporating these methods, risk factors (genetic, environmental, physiologic, sociologic) for the development of diabetes, risk factors for the development of diabetic complications, methods for development of strategies for therapeutic intervention in preventable complications, and assessment of areas with high priority need for epidemiologic research.

This is intended to be a collaborative effort with the World Health Organization, the American Diabetes Association, and the International Diabetes Federation.

Program Announcement of Support for Endocrinology Research

The areas of research supported by the NIADDK's Endocrinology Research Program have been influenced in part by a systematic and comprehensive report, *Evaluation of Research Needs in Endocrinology*, requested by the U.S. Senate and published in 1981. An update or status report enumerating the very considerable research advances of the last 3 years was provided to the Senate in the current fiscal year.

From time to time inquiries are received regarding the kind of work supported by the endocrinology program. A program announcement serves to alert the scientific community to the scope and areas of research supported by the program and stimulates some new and exciting approaches to problems that remain to be solved. It also serves to assure scientists that work in either basic or clinical endocrinology is being supported. This is especially important in times of tight budgets.

During the coming fiscal year, an announcement of the Endocrinology Research Program's support of basic and clinical research in the broad areas of endocrinology will be issued, including research into the cause and treatment of various endocrinopathies, basic research on mechanism of hormone action, production of various hormones either in the body or by artificial means (recombinant DNA techniques, chemical synthesis), and methods of assay and/or isolation of hormones. Support also includes studies on hypothalamic factors, prostaglandins, and other hormone-like materials.

Request for Applications: Need for Research on Autoimmunity in Endocrine Diseases

Publication of a request for research applications would encourage studies of immunology and im-

munogenetics as applied to various of the endocrinopathies and would encourage closer cooperation among scientists of different disciplines.

Thyroid disease is a major disorder that is believed to have autoimmune components, but such studies may also encompass hypoparathyroidism and hypoadrenalism.

At a recent meeting of NIADDK advisors, it was suggested that certain types of studies should be done relating to autoimmunity. The following list of thyroid studies is suggested. Similar studies might be applied to other autoimmune endocrine diseases and include: (1) prospective studies of children at risk for the development of autoimmune thyroid disease to assess the possible ordered appearance of autoimmune phenomena and the relationship to HLA antigens; (2) relationship of manifestations of Graves' disease, its control, long-term remissions, and relapses to HLA antigens, and autoimmunity in relation to exophthalmos and pretibial myxedema; (3) investigation of specific and nonspecific suppressor cell function in patients with autoimmune thyroid disease; (4) development of methods for *in vitro* immunization to assess abnormalities in lymphocytes that may lead to excessive immune responses among patients with autoimmune thyroid disease; (5) characterization and purification of antigens involved in autoimmune thyroid disease; (6) development of methods for producing anti-idiotype antibodies that might be used in therapy; (7) development of clinically useful methods for detecting thyroid-stimulating antibodies.

Stimulation of Research on the Cystic Fibrosis Defect

Much of the basic research sponsored by the NIADDK in CF has been directed toward searching for the so-called CF factor, which has been assumed by many to be a gene product found in the circulation and to be a primary cause of many of the clinical manifestations of the disease. To date, such a substance has not been isolated and characterized, and current studies in this area supported by the NIADDK do not appear likely to achieve this goal in the near future.

Other studies looking for morphological or biochemical anomalies in CF patients have not led to insights into the nature of the defect, often because of the problem of discriminating between primary and secondary characteristics of the disease.

A comprehensive review of the state of knowledge of CF in 1978 recommended that increased efforts be made to stimulate research on the physiological and biochemical processes that appear deranged in the disease, especially exocrine secretion and the factors that control it, and electrolyte and fluid transport in epithelial tissues. A multi-Institute program announcement was published in 1979, and several thousand investigators were directly solicited by mail to apply for research support. This announcement resulted in a tripling of the number of CF-related applications received by NIH; a number of these were funded as part of the Division's regular grant program. More recently, the number of applications received and funded in this area, especially by the NIADDK, has sharply declined.

On the other hand, basic investigational techniques potentially relevant to CF have undergone rapid development. These techniques include improved methods of organ culture, of culturing differentiated tissues, and of investigating intracellular processes involved in the secretion of electrolytes, macromolecules, and water. Molecular biologists have developed methods for searching for specific genetic defects even in the absence of identified defective or missing gene products.

Currently, the NIADDK receives relatively few applications from investigators in the forefront of these areas and fewer still from such individuals who also show awareness that their interests could be related to CF. In order to increase the likelihood that significant progress will be made soon in understanding this prevalent and devastating disease, more first-rate investigators in potentially related areas must be encouraged to address questions of direct relevance to the CF defect.

A New Cystic Fibrosis Center at Case Western Reserve

The Cystic Fibrosis Core Center was initiated at Case Western Reserve University during the past year. It will include the activities of the program project core and in the framework of the awarded budget will also allow for support of pilot and feasibility studies. It is anticipated that regular research project grants grouped around the core center will carry on the excellent research tradition demonstrated by Case Western Reserve scientists associated with the program project. The Medical School and the department of pediatrics at Case Western Reserve have the second largest cystic fibrosis center in the country in terms of patients and therefore are ideally fit to conduct a much-needed multidisciplinary and interdisciplinary approach to the environment of this disease. The support in general administration, communication, program enrichment, patient care, biological samples, pulmonary function studies, computer technology, microbiology, endoscopy, morphology, mucin processing, and central instrumentation are expected to increase productivity of the individual research projects and enhance the probability of realizing the goals of identifying the molecular defect and discovering new and more effective methods of therapy. The transition of the program project to a core center grant enveloped by research project grants should conclude by the early part of 1984.

New Intramural Research Approach to CF

Intramural NIADDK research on CF will be reorganized as an interdisciplinary team, designed to take advantage of the specialized backgrounds of experienced investigators from closely related basic science areas as well as to attract new interest in CF on the part of clinicians who want to acquire research skills. Developed as a special interest of the director of intramural research, the new team is expected to contribute a combination of ideas, the ability to study them in fresh ways, and the ability to pursue trial implementation of promising leads. At the same time, because the team members will be drawn primarily from those not previously engaged in CF research, the team will not be competing for staff members from established CF research centers, and the approach will enlarge the number of workers with experience in this challenging research area.

Cell Lines for Genetic Research in Cystic Fibrosis

The basic biochemical defect in CF remains unknown, and there is no reliable test to detect carriers of the disease (heterozygotes). Thus, a pressing need exists to identify the CF gene so that a test to identify carriers can be developed, and the basic defect underlying the disease can be identified and characterized. Currently, several laboratories are devoting considerable effort to the identification of the CF gene, and other groups have expressed interest in such investigations. What is needed to allow these studies to go forward efficiently is a bank of well-characterized genetic material (DNA) from families in which CF exists. Because relatively large amounts of DNA are required for analysis, transformed lymphocytes are needed (these are white blood cells, stimulated to cell division). Connective tissue cells (fibroblasts) from the same individuals will also be retained in the bank because a considerable literature already describes many of the physiological characteristics of CF fibroblasts, and these familial lines will provide important bases for comparison with previous studies.

For a number of years, the Mutant Human Cell Repository, supported by the National Institute of General Medical Sciences (NIGMS), has maintained a collection of CF fibroblasts, and these lines have been among the most often requested in the repository; however, the collection was not designed as a resource for present-day molecular biologists. This initiative is to make the repository useful to such investigators.

The cell repository is experienced in setting up such special collections, and it has expressed a willingness to work with Institute staff and CF Foundation representatives to locate families and secure material. Twenty-five families will be located that have at least three living children with cystic fibrosis. Blood and skin samples will be taken from all affected and unaffected siblings, both parents, and any available grandparents.

Groups funded by NIGMS and by the Medical Research Council of Great Britain are making significant efforts toward identifying the CF gene, and it is expected that a number of other groups and commercial firms would enter the field if genetic material were readily accessible at modest cost. DNA from the several families that have been identified is in such great demand that transformation of the cell lines is becoming a necessity; the individual investigators who have found and obtained cells from these families do not have the resources to properly maintain and distribute material to all interested and qualified parties.

A Centralized Supply Resource for Human Tissues

The study of normal and diseased human tissue in the laboratory is crucial to understanding many disease mechanisms; however, obtaining such material is a serious problem for many investigators in virtually every area of interest to the NIADDK. In many cases, the acquisition of appropriate tissue for study is a problem because the scientific question being investigated calls for material that may become available at any one location only extremely infrequently. Such situations could be helped by a centralized agency having the ability to procure tissue on a regional or national basis rather than from a single location.

Another problem for investigators is assuring that the tissue they receive has been harvested and preserved in such a way that its study will yield results generalizable to tissue *in vivo*. Often neither a local source of tissue (e.g., a pathologist) nor the investigator him/herself is an expert in methods of preservation, and thus the viability of the tissue being studied may not be well-known. A centralized tissue resource would have as a part of its mission to be fully knowledgeable of the state of the art of tissue preservation and reconstitution and to act as an advisor to investigators in this regard.

It is fully acknowledged that a centralized resource of this kind cannot answer every investigator's needs for human material. For example, some studies of the functional behavior of tissues must be conducted on material which has been removed from the donor no more than 1 or 2 hours previously. Even so, in such a situation, the tissue resource staff could possibly suggest acquisition or preservation procedures conducive to extended viability of tissues.

The National Hormone and Pituitary Program collects human pituitary glands, primarily as a source for the hormone products it distributes.

The National Diabetes Research Interchange, under the sponsorship of the JDF and funded by a grant from the Pew Foundation, was begun in 1981. In its first year of operation it established procurement arrangements with a number of hospitals and other organizations to obtain postmortem tissue, outdated transplant tissue, and surgical waste. It operates exclusively as a brokerage agent and does not store any tissue in its own facility. The NDRI has found that the demand for tissue has been high and that a substantial amount of tissue is available when sources are appropriately approached and developed. In the first 18 months of operation, over 1,500 tissue samples were procured and delivered to investigators. More recently, the NDRI has conducted discussions with investigators from other disease categories (e.g., CF), and pilot efforts are under way to deliver tissues in these areas as well as in diabetes.

The NDRI is clearly demonstrating that a centralized tissue resource can serve the needs of investigators, and its future is currently more certain due to another 3-year grant from the Pew Foundation. It is the objective of this initiative to provide additional stability to funding for a generalized tissue resource that will emphasize the support of research related to the NIADDK diabetes program.

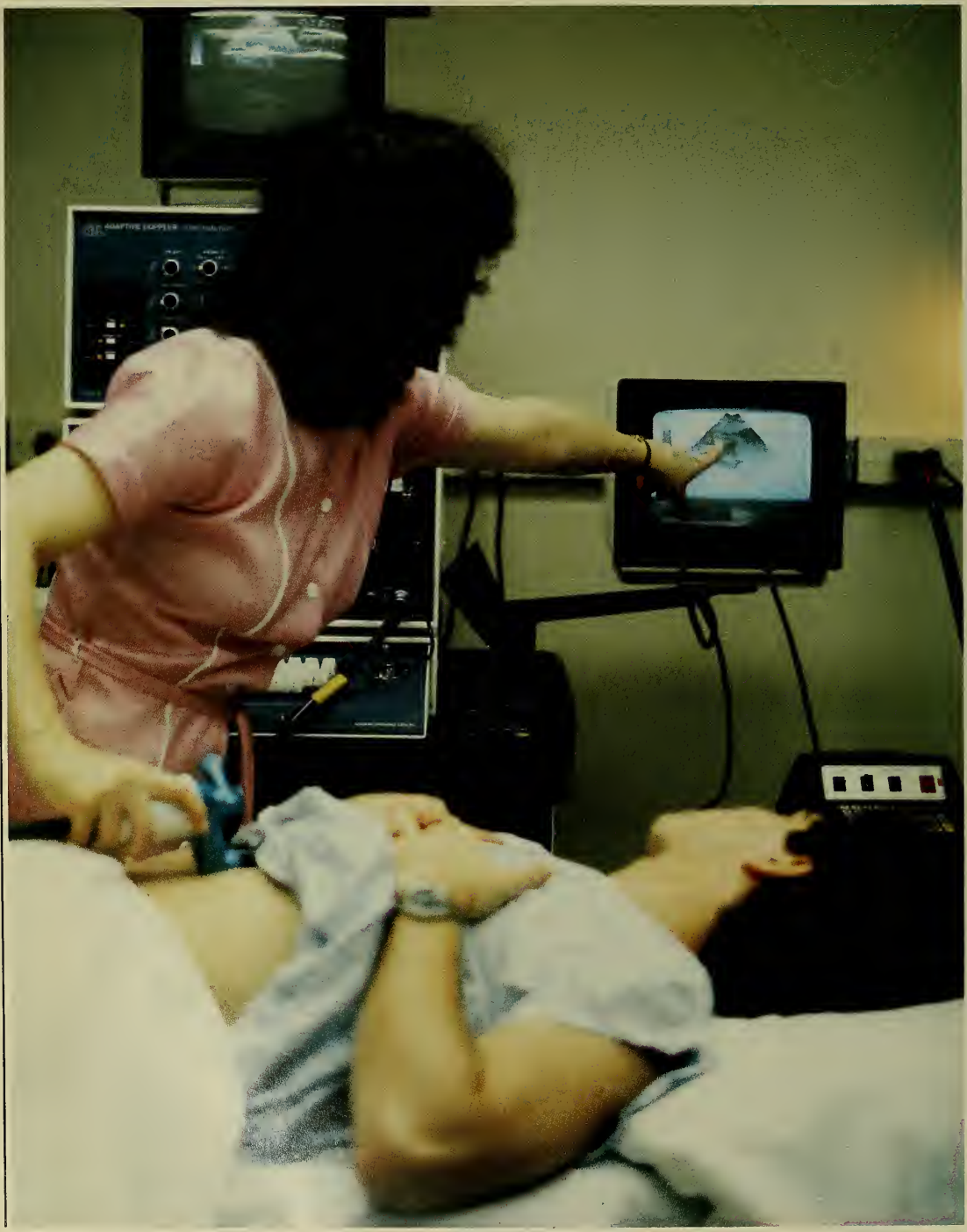
Program Announcements in the Area of Enzymes in Metabolic Diseases

One major goal of the Metabolic Diseases Research Program is to facilitate understanding of enzyme involvement in metabolic diseases within the purview of the NIADDK. Elucidation of the role of gene mutations, posttranslational modifications, and structural manipulations by means of drugs on enzyme function is of paramount importance in our quest to understand, prevent, and cure metabolic diseases due to enzyme defects. This initiative proposes to utilize expert consultants to identify research areas that could benefit from broad-based publicity provided by program announcements.

Initiation of Programs for Small Business Innovation Research Set-Aside Funds

In view of the congressional mandate that NIH target funds for small business innovation research, it seemed desirable that program staff identify and initiate oriented programs for research on inborn errors of metabolism with the aid of specific requests for applications.

For inherited metabolic disorders (e.g., defects of urea cycle enzymes and of purine and pyrimidine metabolism; lysosomal, glycogen and lipid storage diseases; and organic and aminoacidurias), the program is interested in research involving development of diagnostic reagents and assays, purification of relevant enzymes and preparation of antibodies, production of relevant enzymes by recombinant DNA technology, synthesis of substrates for study of enzymes, design and synthesis of chemical activators for mutant enzymes, development of immobilized enzymes for extracorporeal removal of circulating toxic metabolic intermediates, and development and characterization of models for study of various disorders (animal cell lines, mathematical, etc.).



IV. Research Focus—Digestive Diseases and Nutrition

Overview

The Division of Digestive Diseases and Nutrition is responsible for the extramural support of grant awards and contracts pertaining to diseases and disorders of the gastrointestinal tract, the liver, and other associated organs and to nutrition. NIADDK's mission, addressed through this Division's efforts, is twofold—to reduce the suffering associated with these diseases and to reduce their economic impact.

Digestive diseases constitute a health problem of great magnitude. More than 38 million Americans are afflicted with diseases of the digestive system, disorders that exact a high toll in terms of disability, suffering, and economic costs.* Of all the causes of disability due to illness in our country, digestive diseases rank second. Over 2 million Americans are impaired to some degree by these diseases; 1.2 million people are limited in the work that they can perform; and 400,000 are disabled.* Digestive diseases account for 200,000 absences from work each day and are the leading cause of loss of time from work for male employees.* Almost 140,000 veterans receive payments for service-connected disability due to gastrointestinal conditions, at a cost to the Nation of approximately $100 million each year.* But the greater cost is the number of lives lost; digestive diseases cause approximately 200,000 deaths each year (including those associated with malignancies).*

Investigations sponsored by the Division's Esophageal, Gastric, and Colonic Diseases Program and by its Intestinal and Pancreatic Diseases Program are directed at the structure, function, and diseases of the esophagus, stomach, small and large intestines, anorectum, pancreas, and salivary glands. Of particular concern are heartburn and esophagitis, hiatus hernia, gastritis, peptic ulcer disease, diverticulitis, ulcerative colitis and Crohn's disease, intestinal malabsorption syndrome, sprue, diarrhea, functional disorders including spastic colon, acute and chronic pancreatitis, and Zollinger-Ellison syndrome. Also included are general studies of the gastrointestinal hormones.

Through its Liver and Biliary Diseases Program, NIADDK supports studies of the structure, function, and diseases of the liver, biliary tract, and gallbladder. Included in these studies are inflammatory, toxic, metabolic,and genetic diseases of the liver such as hepatitis, cirrhosis, Wilson's disease, primary biliary cirrhosis, fatty liver, hepatic encephalopathy, Dubin-Johnson syndrome, and Gilbert's disease. Other investigations focus on liver regeneration, liver assist (artificial liver) devices, and liver transplantation, as well as liver ischemia, portal hypertension, and toxic liver disorders. Biliary and gallbladder studies are directed at cholestasis, pigment and cholesterol gallstones, and the metabolism of bile and bile salts.

The Nutrition Program of NIADDK continues to foster and support research and training in the broad areas of fundamental and clinical nutrition. Nutritional factors and diet are believed to play a significant role in 6 of the Nation's 10 leading causes of death: heart disease, stroke,

* National Commission on Digestive Diseases.

NIADDK emphasizes nutrition research to ameliorate the effects of malnutrition-related disorders such as iron deficiency anemia, night blindness, and obesity. As part of this research, food portions are weighed and analyzed for their nutrient compositions.

Facing page
The development of noninvasive techniques (such as ultrasound) for visualizing the gastrointestinal tract has enabled NIADDK researchers to refine treatments for disorders such as gallstones and pancreatitis. Such techniques also reduce the exposure of patients to X-rays.

cancer, diabetes, atherosclerosis, and cirrhosis of the liver. Nutrition research has traditionally been an important area of interest for NIH in general, and for NIADDK especially. The common occurrence of nutrition-related diseases or conditions such as obesity, anorexia nervosa, bulimia, diabetes, osteoporosis, alcoholism, anemia, and atherosclerosis in segments of the U.S. population attests to the need for a better understanding of the role of nutrients in these clinical problems. The greatest promise for solutions to such problems lies in fundamental research on the mechanism of action of specific nutritional factors and nutrient interactions, and on the role of diet or nutrients as metabolic regulators and physiological modifiers of behavior. The Nutrition Program continues to stress the following priority research areas: (1) fundamental studies on the metabolic role of specific dietary components, including essential amino acids, protein, vitamins, minerals, essential fatty acids, fats, carbohydrates, and metabolizable energy; (2) investigation of the underlying causes of obesity, with the aim of developing appropriate methods for prevention and control; (3) studies on nutritional requirements in health and disease with emphasis on individual and environmental differences; (4) studies on the nutritional support of the patient as it affects nutritional status of the whole individual with such conditions as obesity, surgical trauma, burns, or chronic renal failure; (5) basic studies on the role of dietary fibers on transit-time digestion, rate of absorption, intestinal microflora, and interactions with nutrients, drugs, bile salts, and other substances; and (6) research on nutrition and infection and immune competence.

Recent technological advances, including mass spectrometry (using stable isotopes), high-pressure liquid chromotography, radioimmunoassay, and rapid analysis of amino acids and trace metals, offer promise for rapid progress in such basic nutrient-focused studies in human health.

Highlights of Research Advances

The following sections briefly highlight areas in which the Division of Digestive Diseases and Nutrition has reported recent progress in its research programs.

- Advanced cirrhosis of the liver frequently results in development of venous varices in the esophagus. Hemorrhages from such esophageal varicose veins constitute a serious gastrointestinal emergency. A group of investigations now reports successful treatment of such varices by injecting them with a sclerosing solution through an endoscope. With time, the treated veins are absorbed by the body and disappear.
- A new drug for treatment of peptic ulcer, ranitidine, is very effective in inhibiting gastric acid secretion and has been reported free of the feminizing side effects sometimes seen from the use of cimetidine.
- The inflammatory bowel diseases, ulcerative colitis and Crohn's disease, involve antibodies formed against the patient's own intestinal lining cells (autoimmunity). Normal bacterial antigens in the intestine may aggravate this effect if they cross-react with intestinal cell antigens.
- Somatostatin, one of the hormones present both in the intestine and in the brain, can inhibit diarrhea and conserve the patient's needed electrolytes (such as sodium and chloride).
- Major advances in liver transplantation have led to a significant increase in the survival rate of transplant recipients. These include improved surgical techniques and more effective immune suppression to prevent rejections, especially with the promising new agent cyclosporine.
- Further confirmation has been obtained of the link between chronic active hepatitis and liver cancer.
- The presence of alcoholic liver disease may be signaled by a dramatic drop in vitamin A levels in the liver, before extensive damage has occurred.
- Patients with primary biliary cirrhosis (a serious chronic destructive liver disease) show increased levels of antigen-antibody complexes in the circulation, pointing to a previously suspected immunologic basis for the disease.
- Studies in patients fed for prolonged periods with the aid of total parenteral nutrition (by vein) have led to the discovery of several previously unknown nutritional deficiency syndromes caused by the lack of specific trace minerals—which had not been recognized in the past as nutrients essential for normal health.
- A new rapid test of dark adaptation (night blindness), suitable for use under field conditions, has been developed as a reliable tool to screen for vitamin A deficiency.
- In postmenopausal osteoporosis, a serious bone-thinning disease afflicting millions of people, improved calcium retention and decreased bone fracture rate can be achieved with use of metabolite of vitamin D (1,25-dihydroxyvitamin D_3).
- Although they may be active under test-tube conditions, it has now been reported that starch

blocker diet tablets are not able to inhibit the digestion of starch in normal use in man.

- A new method for the determination of total body fat and lean tissue mass, the TOBEC method, is both rapid and noninvasive. It is based on total body electrical conductivity and lends itself to screening for nutritional status and body composition.

Digestive Diseases

Gastrointestinal Peptide Hormones Affect the Brain Also

Prior Findings

During the past two decades a series of remarkable advances have occurred in the understanding of gastrointestinal physiology. These advances are due in large measure to identification of an increasing number of gastrointestinal peptides, which have demonstrated varied pharmacological properties. Many of these peptides have been shown to interact with specific receptors on cells in the gastrointestinal tract, and to have significant hormonal effects in digestive processes, and have provided considerable support to the concept of the digestive tract serving as an endocrine organ system. Perhaps what is even more intriguing is that hormones previously thought to act only on the digestive system have been found to affect the central nervous system (CNS) as well and are found in both locations. It seems increasingly likely that the brain contains virtually every peptide found in peripheral tissues.

An interesting example is cholecystokinin (CCK), in its relationship to regulation of appetite and to obesity. Cholecystokinin is the parent molecule of a family of polypeptide hormones, some of which are secreted into the circulation from the small intestine after eating. This compound stimulates both secretion of the exocrine pancreas (into the intestine, via the pancreatic duct) and contraction of the gallbladder. CCK-like molecules have also been identified in the central and peripheral nervous systems. The biological significance of CCK in the brain has yet to be determined.

Recent work by NIADDK grantees has provided new evidence for a specific central nervous system role for CCK. The investigators prepared a special complex of CCK that binds to specific receptors in the brain and pancreas of mice and undertook a study to determine whether CCK receptors in the animals' brains were influenced by fasting. In a comparison of fed mice and 42-hour-fasted mice, fasting significantly increased CCK binding to its receptors in the olfactory bulb (by 46 percent) and hypothalamus (by 42 percent), but not in other brain regions. The increase was shown to be a result of an increase in the number of receptor sites.

The discovery that fasting leads to an increase in CCK receptors in the hypothalamus, which has been shown in several species to regulate appetite, supports the concept that CCK may control satiety through interaction with the region of the brain. Continued research may have implications for weight control and weight reduction in obese persons. Other NIADDK grantees have reported that the intravenous infusion of another CCK-like molecule will shorten the duration of each meal in both lean and obese human subjects and thus result in the consumption of considerably less food during meal sittings.

Recent Advances

Regulatory peptides that affect gastrointestinal function may also affect the CNS. For example, at least eight such substances, including CCK, are known to stimulate growth hormone release from the pituitary gland. Illustrative actions of some peptides now identified as having CNS roles include:

- Vasoactive intestinal peptide, which produces release of pituitary hormones (growth hormone, prolactin, and luteinizing hormone) and causes hyperthermia (elevated body temperature) in cats.
- Somatostatin, which causes sustained suppression of certain pituitary hormones (growth hormone and thyroid-stimulating hormone).
- Bombesin, which produces hyperthermia when injected into the brain spinal-fluid cavities (cisternae).
- Substance P, which heightens pain perception, stimulates pituitary growth hormone release, suppresses drinking, and produces hypothermia.
- Enkephalins, which cause pain suppression (analgesia) as well as behavioral changes, hyperthermia, vomiting, stimulation of pituitary growth hormone and prolactin (luteotropic hormone) release and suppression of pituitary luteinizing hormone and follicle-stimulating hormone release.

Additional studies have been carried out to characterize the primary structures (amino acid sequences) of the peptides mentioned above and to synthesize labeled peptides (for use as molecular probes).

Research Directions

Production and use of synthetic probes will permit the further study of cell membrane receptors of these peptides and provide a clearer understanding of hormone-receptor interactions. With the recent

availability of many peptides or hormones and assay methodologies, studies can now be initiated with the long-term goal of characterizing the actions of gut and brain peptides on the central neural control of the gastrointestinal tract, identifying their mechanisms of action, and determining their physiological roles in the regulation of gastrointestinal function.

Studies of the brain and the digestive system have led to a better understanding of how gastrointestinal function is integrated. Studies of hormonal regulation at all levels of the digestive system are continuing, and solid progress is being made. Understanding the relationship between the CNS and the digestive system may provide an insight into the basic mechanisms of many digestive diseases, including functional bowel disease (bowel dysfunction).

Control of Esophageal Hemorrhage

Prior Findings

Cirrhosis of the liver is a major cause of morbidity, mortality, and health-care expense, but an effective form of therapy has not been developed as yet. In cirrhosis, when venous pressure rises in the liver, collateral channels (varices) develop in an attempt to return blood to the systemic venous circulation. These varices tend to develop in the submucosa of the esophagus and stomach, where they pose the problem of rupture. The frequency of varices in cirrhotic patients varies from 14 percent to as high as 77 percent, depending on the type, duration, and severity of the cirrhosis. Although the direct injection of the individual varices with a sclerosing agent to thrombose the vessels was first described in 1939, it remained unnoticed until 1955, when the procedure was used in the United Kingdom. Shunt (bypass) surgery dominated portal hypertension therapy in the 1950's and 1960's, and sclerotherapy waned. There has been a gradual disenchantment with shunt surgery because of its resultant high morbidity and mortality, and injection sclerotherapy is enjoying a revival.

Recent Advances

Investigators from Cape Town, South Africa, have achieved control of acute esophageal bleeding in 95 percent of the patients admitted to the hospital for this life-threatening emergency. Through an endoscope passed into the esophagus, they injected the bleeding varices with a sclerosing solution, such as 5 percent sodium morrhuate, which thromboses and eventually obliterates the injected varicosity. A single injection sufficed to control the acute bleeding in 70 percent of patients; repeated injections permitted control of 95 percent of these emergencies. Preliminary studies in other centers confirm these findings. Moreover, repeated injections have been found by this group to *prevent* repeated bleeding episodes for 1 year or longer in the majority of patients (30 of 52 with repeated injections versus 14 of 56 without). An exciting finding was the complete disappearance of both gross esophageal and gastric varices even though only the esophageal varicosities were injected. The procedure as performed in the United States uses a flexible fiberoptic endoscope without anesthesia, whereas the Cape Town group advocates the rigid endoscope with anesthesia.

Research Directions

Sclerotherapy may offer a means of preventing bleeding that does not involve major surgery. Although presently sclerotherapy is being used only after a bleeding episode occurs, prophylactic injection for patients who have not yet bled from their varices may be justified in the future, if the technique is confirmed to be relatively safe and if patients at high risk for a first variceal bleeding episode can be identified. Further research in this direction is continuing.

Reflux Esophagitis: A New Monitoring Device

Prior Findings

Esophagitis, or irritation and inflammation of the esophagus, constitutes a significant cause for discomfort in many Americans. The most common cause of esophagitis is the retrograde propulsion of gastric contents into the terminal end of the esophagus. Symptoms associated with this phenomenon are commonly known as heartburn. At the junction of the esophagus and the stomach is a muscular portion of the esophagus known as the lower esophageal sphincter (LES). The inability of the sphincter to remain closed when the stomach is full is known to contribute to the reflux of the acidic gastric contents into the esophagus, causing esophagitis.

The underlying reasons for the inappropriate relaxation of the sphincter are not fully understood. Two teams of NIADDK grantees have found that two distinct classes of chemical compounds cause relaxation of the LES. One substance, a peptide hormone known as vasoactive intestinal peptide, is released in the LES area when the vagus nerve is stimulated. The other compound, morphine, reduces LES pressure by acting on the central nervous system. It is possible, therefore, that naturally occurring morphine-like compounds (endorphins) in the central nervous system are involved in the physiological control of pressure on the LES.

Regardless of the cause of the problem, it is desirable to be able to monitor variations in sphincter pressure to understand when such variations are physiological

and when they are pathological and to relate the effect to the possible causes.

Recent Advances

Institute grantees have attacked successfully a problem that heretofore had confounded the measurement of the lower esophageal sphincter pressure (LESP). The movement of the esophagus caused by expiration and inspiration normally produces wide variances in experimental LESP measurements. A component was developed for fusing a special sleeve device to the conventional catheter assembly for measuring LESP.

Incorporating this modified pressure sensor with a catheter assembly, in which acidity (pH) could also be measured, investigators were able to generate considerable information about the patterns of LESP and reflux that appear in patients with esophagitis as compared to those patterns in controls. For example, the device was placed in the esophagus for 12-hour periods, and changes in LESP and changes in the frequency of reflux episodes were measured following a meal. As would be expected, the 12-hour, overnight studies confirmed that healthy control subjects, as well as esophagitis patients, had episodes of gastro-esophageal reflux; the patients, however, had a significantly greater number of reflux episodes per 12-hour interval than the controls. For both groups, reflux frequency increased after eating, suggesting that gastric volume plays a role in promoting reflux. The reflux rate tapered off dramatically over 11 hours, dropping to a frequency of about 1.4 each hour in patients and 0.2 each hour in control subjects.

Research Directions

The availability of a new technology for monitoring variations in gastroesophageal sphincter pressure will facilitate further research on mechanisms of reflux esophagitis. By permitting reliable and accurate measurement of pressures under a variety of experimental and clinical conditions, the technique will aid both the diagnostic and the therapeutic applications of research findings to this pervasive source of human discomfort and illness.

Drug Therapies for Peptic Ulcer

Prior Findings

Duodenal ulcers affect a large percentage of the population and account for many days lost from work and high health costs. In recent years, Institute grantees have demonstrated the effectiveness of certain antihistamines and prostaglandins in blocking or inhibiting gastric acid secretion in patients with peptic ulcer. Between 1970 and 1978, hospital admissions for duodenal ulcer decreased by 43 percent, and deaths from peptic ulcer decreased by 31 percent, partly due to the use of the new therapeutic agents. Improvements have also been made in conventional antacid therapy.

Another approach to the treatment of ulcers has been study of the factors governing the secretion of the protective mucus that bathes the inner linings of the stomach and intestine and the repair and regeneration of the mucosa. Some drugs, such as sucralfate, have a protective effect on the mucosa. Sucralfate is a basic aluminum salt of sucrose sulfate, with sustained protective effects against pepsin, acid, and bile at the site of a peptic ulcer.

Studies on histamine and its role in gastric acid secretion have led to the development of two important antiulcer agents: cimetidine, presently in widespread use, and ranitidine, which has been approved recently by the Food and Drug Administration.

Cimetidine, a histamine (H_2)-receptor antagonist, is an effective drug for healing peptic ulcers and for preventing their recurrence; however, it can produce certain antiandrogenic side effects, such as gynecomastia (enlargement of the breast) and sexual impotence, in male patients receiving relatively large doses of the drug.

Recent Advances

In a carefully controlled evaluation of cimetidine for the healing of uncomplicated gastric ulcer, an NIADDK-supported study compared the drug's use with low-dose antacid and with a placebo (sham medication). Patients with bleeding, obstruction, perforation, concomitant duodenal ulcers, or evidence of cancer were not included. The results showed that cimetidine produced healing in 53 percent of patients in 4 weeks, rising to 89 percent by 12 weeks (but almost as good at 8 weeks). The antacid produced healing in 38 percent in 4 weeks, rising to 84 percent by 12 weeks. In the placebo group, the comparable figures were 26 percent rising to 70 percent. Healing was judged by appearance at endoscopic examination. The response to cimetidine was significantly better than to the placebo; it definitely hastened the healing process. For relief of *symptoms*, however, neither cimetidine nor antacid was more effective than the placebo. The presence or absence of symptoms was not a reliable indicator of the presence or absence of a gastric ulcer.

In another study, an intramural NIH research team evaluated cimetidine's tendency to cause clinically important antiandrogenic side effects and studied the usefulness of the newer antihistaminic agent, ranitidine, as an alternative therapy. Twenty-two patients were studied. Of these patients, 20 had Zollinger-Ellison syndrome, a disease characterized by a marked increase in gastric acid secretion and peptic ulcers

caused by gastrin-secreting pancreatic islet cell tumors. Two had gastric hypersecretion of unknown cause. To control excess acid secretion, these patients were receiving cimetidine in doses approximately 3-1/2 times those used in the treatment of regular duodenal ulcers.

Of the 22 patients followed and evaluated, 11 complained of recent onset of antiandrogenic symptoms: 9 were sexually impotent, 9 had breast changes, and 7 had both. The remaining patients showed no symptoms. The 11 patients who developed impotence and/or breast changes did not differ significantly from those patients who did not develop side effects, in age, acid output, serum gastrin levels, or time treated with cimetidine. They did receive higher doses of cimetidine, but their doses did not differ by a statistically significant amount from those of patients without side effects. These studies also demonstrated that the impotence associated with cimetidine was organic rather than psychogenic.

Ranitidine is a new histamine (H_2)-receptor antagonist reported to have no such antiandrogenic side effects. In 9 of the 11 patients with side effects, cimetidine was discontinued, and therapy with ranitidine begun. In each of these patients, the undesirable side effects disappeared.

Because of its lack of antiandrogenic side effects and its effectiveness in inhibiting gastric acid secretion, ranitidine appears to be a preferable histamine (H_2)-receptor antagonist in the treatment of male patients with gastric hypersecretory states.

Research Directions

In view of the successful use of cimetidine, especially in the healing of gastric ulcers, research should be directed toward conditions of its use that avoid the side effects associated with it. Adjustment of dosage, use in combination with other drugs, and synthesis of closely related compounds are some of the alternatives that should be explored. Study of the mechanism by which its antiandrogenic effect is produced may lead to ways of modifying this undesirable action.

In view of the promise of ranitidine as a safe and effective antihistamine for healing peptic ulcers and preventing their recurrence, its further evaluation is indicated, to verify and extend findings to date and to determine optimal clinical conditions of its use. Synthesis of compounds structurally related to ranitidine may identify even more effective or longer acting drugs equally free of side effects.

Treatment of Hemorrhagic Gastritis

Prior Findings

Hemorrhagic gastritis is an inflammation of the stomach lining with hemorrhaging. It is a life-threatening condition associated with such stressful precursors as severe trauma, extensive burns, infection (sepsis), low blood pressure, or failure of the lungs, kidneys, or liver. Treatment with antacids or cimetidine, along with flushing with iced water, has not been very satisfactory in reducing the risk of serious illness and death.

Studies in animals have shown that the hormone-like fatty acid derivatives known as prostaglandins (specifically, structures similar to prostaglandins of classes A, B, E, F, and I) can be effective in preventing acute gastric erosions induced by such stressors as alcohol, strong alkali or acid, bile salts, aspirin, and bacterial sepsis.

Recent Advances

Experimental success with prostaglandins led an NIADDK-supported team to use 15-methyl-prostaglandin E_2 (PGE_2) in a patient with sepsis and acute bleeding unresponsive to antacids, cimetidine, and other supportive drug treatment. Immediate and lasting cessation of hemorrhaging resulted. The dosage used was 50 micrograms every 6 hours preceded by a mild acid, to convert the prostaglandin to its most active form, and followed in an hour by an antacid. After 6 days, the gastric lining was almost normal on visual (endoscopic) inspection. Treatment continued for 10 days. A year later the patient remained in excellent health.

Research Directions

It is necessary to conduct well-controlled clinical studies of this prostaglandin E_2 derivative, treating additional cases of unresponsive hemorrhagic gastritis, before it can be assumed that the substance is appropriate for general clinical use. Such studies could show undesirable side effects connected with its use or confirm their absence. Further study of the mechanism of the protective effect of this and related prostaglandins on the gastric lining is necessary, both to understand the basis of their action in this disease and to suggest other applications for the treatment of disease.

Sensitivity to Dietary Gluten: Genetic Control of Immunological Responses

Prior Findings

Gluten-sensitive enteropathy (GSE; celiac disease or nontropical sprue) is a disease that affects the mucosa (mucus-secreting lining) of the small intestine and results in the malabsorption of most nutrients.

Patients with this disorder have poor intestinal absorption and excessive elimination of unabsorbed dietary substances following ingestion of gluten-containing foods such as wheat, rye, oats, and barley. An associated feature of this gluten enteropathy is a lesion of the small bowel—flattening and erosion of the mucosa.

The disease is known to be activated by protein(s) in the gliadin fraction of wheat gluten. A purified alpha-gliadin fraction (A-gliadin) has been shown to bring about the lesion of GSE in susceptible individuals. The mechanism of cell damage to the intestinal lining and of loss of normal mucosal architecture is not known; however, immunological mechanisms appear to be operating. The evidence for an immunological cause is indirect: (1) the epithelial cell layer is infiltrated by lymphocytes and a deeper layer (the lamina propria) by plasma cells; (2) there are reports of increased antibody synthesis by the mucosa, in response to a variety of dietary antigens and components of gluten in patients with GSE; and (3) genetic chromosomal regions known to be involved in immunoregulation, especially the major histocompatibility complex areas HLA-Dw3 and HLA-DRw3, occur with greater frequency in patients with GSE.

Recent Advances

Under NIADDK support, investigators have examined the genetic control of the circulating antibody response to purified A-gliadin in the mouse. Using inbred strains of varying degrees of genetic homogeneity and sensitive assays developed in their own laboratory, these investigators found that the humoral antibody response to A-gliadin, which is dependent on thymus lymphocytes (T cells), is under the control of genes mapping to the major histocompatibility complex region of the chromosome. This suggests that the sensitivity to dietary gluten found in patients with GSE may be genetically controlled in a similar manner—that is, that T-cell-dependent humoral antibody and T-cell-mediated immune responses to gliadin in the diet of individuals sensitive to it may be determined by specific genes concerned with the regulation of immunity.

Research Directions

Work should now be directed to the nature, regulation, and specificity of the immune response to the gliadin proteins that cause gluten-sensitive enteropathy, so that ways of modifying this response can be developed. In view of the probable genetic basis for the response, the possibility is raised that the mechanism of its harmful expression in victims of the disease may be subject to control or even to repair of an underlying defect. This possibility can be explored only by further basic research on the disease and its mechanisms.

Autoimmune Responses in Inflammatory Bowel Disease

Prior Findings

Two inflammatory bowel diseases (IBD's) of unknown etiology, ulcerative colitis and Crohn's disease, appear to be associated with abnormalities of the body's immune system. This theory is based on the observations that these IBD's occasionally occur with other immunologically mediated conditions, by immune-related concomitants of the diseases, by their favorable therapeutic responses to adrenal corticosteroids (which are immunosuppressive), and by the rich immunologic resources and immunologic responsiveness of the gastrointestinal tract.

Evidence suggests that, regardless of the primary causative agent or factor in inflammatory bowel disease, certain immune processes in the body play a part in the persistence or chronicity of the disease. Among the immunologic disturbances found in patients with Crohn's disease or ulcerative colitis are high levels of antibodies to cells lining the intestine and the apparent cytotoxicity (cell-killing activity) of circulating lymphocytes (white blood cells) for these epithelial cells.

Recent Advances

Institute-supported studies have shown that the cytotoxicity of circulating lymphocytes to the cells lining the colon is seen only in patients with inflammatory bowel disease and is specific to the colon. The effect occurs with cell-free extracts of lymphocytes and takes place rapidly, without the need of other immune-assisting proteins (of the complement series of blood proteins). Blood serum from patients with ulcerative colitis can induce the cytotoxic property in normal lymphocytes incubated in it. This property can be abolished or diminished in the lymphocytes of a patient with ulcerative colitis if they are first incubated in the patient's own serum, which confirms the presence of autoimmune (self-reacting) antibodies. Finally, there is evidence that antigens from bacteria normally in the intestine can stimulate the cytotoxicity, if these antigens cross-react with (are similar to) the antigens of the cells lining the patient's colon.

Research Directions

Further work on autoimmune mechanisms in inflammatory bowel diseases is desirable and will lead to a clearer understanding of their true role in these

diseases. Knowledge of the disease mechanisms, in turn, may then be translated into new approaches to therapeutic intervention.

Somatostatin Inhibits Diarrhea and Saves Electrolytes

Prior Findings

Somatostatin is a peptide hormone known to be elaborated in the intestine and pancreas and in the hypothalamus region of the brain. It suppresses secretion of growth hormone by the pituitary gland. Recently, it has been found also in both mucosal endocrine cells and neurons in the intestine; therefore, it may function as a neurotransmitter or have a paracrine (local) effect in the intestine. In addition, it may function as a circulating hormone. Somatostatin has now been shown to affect a variety of intestinal functions. It inhibits gastric acid secretion, pancreatic enzyme and bicarbonate secretion, intestinal motility, and splanchnic (regional intestinal) blood flow. It also inhibits the release of hormones or neurotransmitters such as vasoactive intestinal polypeptide, gastric inhibitory polypeptide, gastrin, and secretin that may contribute to diarrhea.

Recent Advances

Since somatostatin is present in the intestine and affects a variety of intestinal functions, it seemed likely that it also had a direct effect on intestinal electrolyte transport. Studies were carried out in laboratory animals to determine its effect on electrolyte transport, its mode of action, and potential therapeutic application of this peptide. It was found that somatostatin could stimulate sodium and chloride absorption in the rabbit ileum and that it could also inhibit the effect of secretion-inducing agents (secretagogues) in the rat jejunum, ileum, and colon.

The ability of somatostatin to reverse or prevent secretagogue-induced secretion in the rat jejunum and ileum suggests that this peptide may be therapeutically useful in secretagogue-induced diarrhea. Investigators have infused somatostatin into a patient with the carcinoid syndrome and watery diarrhea. (A carcinoid is a rare tumor with a distinct appearance and location, most often in the small intestine in the region of the appendix. The tumor produces biologically active substances such as serotonin, histamine, and epinephrine-like compounds, which can cause acute severe vascular changes along with diarrhea and other symptoms.) During the somatostatin infusion, diarrhea ceased, and there was a dramatic decline in stool weight and electrolyte content. These results have been confirmed by another laboratory in another patient with secretory diarrhea due to malignant carcinoid syndrome.

In view of somatostatin's ability to (1) stimulate electrolyte absorption in the isolated rabbit ileum and water and electrolyte absorption in a patient with severe secretory diarrhea due to malignant carcinoid syndrome, (2) inhibit secretagogue-induced water and electrolyte secretion in the intact rat jejunum and the isolated rat colon, (3) decrease intestinal motility, (4) inhibit the release of hormones or neurotransmitters that may contribute to diarrhea, and (5) inhibit diarrhea in patients with carcinoid tumors and short bowel syndrome, it might be a clinically useful therapeutic agent in the treatment of diarrheal syndromes.

Research Directions

The development of compounds with somatostatin-like effects for use in control of diarrhea should be pursued, with initial attention to introducing changes in the molecule that would make the new synthetic product freer of side effects and active in the oral form. An oral form is necessary for the conduct of longer term studies. Somatostatin affects many organ systems and, thus, has many side effects that limit its use in any one specific clinical situation; therefore, attempts must be made to develop a gut-specific somatostatin analogue with fewer side effects.

Hepatitis and Cancer

Prior Findings

It is now known that years after a person is infected with hepatitis B virus (HBV), a chronic carrier state can develop, leading to chronic active hepatitis and, as epidemiologic and other evidence suggests, an increased risk of liver cancer. There are about 180 million carriers of the virus worldwide (some 750,000 in the United States).* Because chronic active hepatitis occurs in 1 to 5 percent of the carrier population, and because there is evidence that these individuals are at increased risk for liver cancer, it is important to learn how unresolved hepatitis may become malignant.

The epidemiological link between HBV and hepatocellular cancer (HCC) has been strengthened by large studies in Japan and China—but not in this country, where its incidence is much lower. A study of 2,985 Tokyo workers followed for 5 years showed a 28-fold increase in deaths from HCC when HBsAg-positive (hepatitis B "s" antigen) individuals were compared with controls. In 20,000 Chinese workers, the findings were similar.

With advances in recombinant DNA and other techniques of modern molecular biology, scientists have now been able to investigate at the molecular

* American Association for the Study of Liver Diseases.

level—using small amounts of tissue from liver biopsy samples—genetic changes from one stage of infection to another. Last year, Institute grantees showed that once hepatitis B virus affects liver cells, the viral DNA may genetically reprogram the invaded host cells; this process is called integration of DNA into the genetic apparatus (genome) of the host cell. Human carriers of HBV are showing integration of viral DNA into the liver genome when the carrier state is of long duration, but not in the short term.

Recent Advances

There is additional evidence that hepatocellular carcinoma probably develops in certain long-term carriers with chronic hepatitis B at least partially as a result of the integration of viral DNA into the liver-cell genome.

In human liver biopsy specimens from chronic active HBV carriers, viral DNA was found in a free form in the nucleus of five carriers who had evidence of the carrier state for less than 2 years, whereas in five long-term carriers, HBV DNA was found to be integrated into the genome of the liver cell. In human primary hepatocellular carcinoma, the DNA extracts from all tumors coming from patients who were HBV carriers showed HBV DNA integrated into the host genome. This work, performed by an NIADDK grantee as part of a liver center pilot project, has now been confirmed by a group of French investigators.

Research Directions

Research that sequentially follows all stages in viral hepatitis B infection, from onset of acute hepatitis to chronic liver disease and possibly to liver cancer, is now feasible. Such studies may be useful in identifying viral hepatitis carriers at high risk of developing primary liver cancer. Using the integration state as an endpoint, scientists also have the opportunity to access the ability of drugs such as corticosteroids to prevent the progression from the unintegrated to the integrated state in patients with chronic active hepatitis of viral origin.

Liver Vitamin A Levels in Alcoholic Injury

Prior Findings

Symptoms of vitamin A deficiency may occur in alcoholics; further, cirrhosis due to alcoholism is associated with low levels of circulating vitamin A. Alcoholic hepatitis is often associated with evidence of damage to the liver known as Mallory bodies, which stain like the hard protein material of hair and nails (keratin); vitamin A deficiency is associated with keratin abnormalities in other tissues.

Recent Advances

Alcoholic liver disease often causes severe depression of vitamin A levels in the liver, at a stage before extensive liver damage and Mallory bodies have occurred and when blood levels of vitamin A and its associated blood proteins are still unaffected. This can happen when the diet is normal and even when the diet is enriched with vitamin A.

Research Directions

More work needs to be done on the mechanism by which alcoholic liver disease is associated with lowered hepatic vitamin A, on whether vitamin A should be administered to these patients, and, if so, on the proper dose level to ensure correction of the deficiency without toxicity to the liver from excess vitamin A.

Liver Collagen Formation, Fibrosis, and Cirrhosis

Prior Findings

Collagen is the major protein component of the matrix of the liver (the substance between the cells). It is synthesized by fibroblasts, the cells that form connective tissue, but evidence from NIADDK-supported studies has shown that the major liver cells themselves (the hepatocytes) also synthesize collagen, under conditions that rule out the presence of other possible sources of the new collagen.

Recent Advances

Using a method of identification of types of collagen present in rat tissue samples by staining them with specific antibody reactions, investigators have extended their work on the hepatocyte by showing that at least three types of collagen are synthesized. Prominent among these is the major component of the basement membrane (the fine layer at the base of the cell), a finding significant because this membrane thickens in regenerating liver and in cirrhosis. The three collagens appeared in a sequence that suggested they may be important contributors to the process of fibrosis in the liver, which can ultimately progress to cirrhosis.

Research Directions

Now that the role of the hepatocyte in repairing injury to the liver by formation of new collagen, leading to fibrosis, has been confirmed, further research must

examine the processes of liver cell injury and repair, fibrosis, and cirrhosis, in order to understand them better and possibly to prevent their harmful and often fatal consequences.

Primary Biliary Cirrhosis: Immune Complexes in the Circulation

Prior Findings

Primary biliary cirrhosis is a chronic, progressive, and often fatal disease of unknown cause with (usually) slowly progressive destruction of the bile ducts inside the liver, in the absence of bacterial-type infection. The patterns of inflammation and antibody formation suggest that immunologic mechanisms are involved and, indeed, circulating complexes of antibodies with (unidentified) antigens have been found in 60 percent of patients with the disease. Such complexes correlate significantly with levels of antibodies against a patient's own mitochondria (the subcellular organelles concerned with cell respiration and energy production and balance) and with the severity of the inflammatory process surrounding the bile ducts.

Recent Advances

In a 3-year study of 88 patients with primary biliary cirrhosis, patients with evidence of antibodies against their own tissues (autoimmunity) and those with associated diseases thought to have an autoimmune basis (rheumatoid arthritis, scleroderma, and others) had an increased prevalence of circulating immune complexes (of unidentified antigen plus antibody) and increased levels of the complexes. The levels of these complexes of antigen with antibody decreased (or remained normal, if not elevated) when patients were treated with the drug D-penicillamine; whereas, in a control group without the drug, they consistently increased. The immunologic mechanism appears to involve the complement system—a system of serum proteins acting together with antibodies to reinforce immunologic defenses. Significantly, the levels of complexes increased as the disease worsened (by clinical, blood, or tissue signs) and decreased as patients improved.

Research Directions

The significance of circulating immune complexes for the mechanisms of disease needs to be established not only for primary biliary cirrhosis but for other diseases with inflammatory tissue reactions on an immunologic basis, in the liver, kidney, joints, and other tissues. Identifying the nature of the antigens present in these complexes is important for better understanding and treatment or prevention of these diseases. In primary biliary cirrhosis, more than one antigen-antibody system seems to be involved.

Primary Biliary Cirrhosis: Severity and Clinical Outlook

Prior Findings

Primary biliary cirrhosis is found in about 50 of every 1 million people and is suggested by the presence of jaundice, itching, lipid nodules in the tissues, and easy fatigability. Without the appearance of these features, the diagnosis can be suspected if there is evidence of liver abnormalities (unexplained enlargement and blood serum enzyme levels showing tissue damage) and mitochondrial antibodies in the blood serum and can be confirmed by a biopsy of liver tissue. If the disease progresses to cirrhosis (scarring of the liver), it frequently leads to death from liver failure or hemorrhage (due to back pressure from the scarred liver enlarging the veins in the esophagus).

Recent Advances

In a study of 280 patients with a confirmed diagnosis of primary biliary cirrhosis, the average length of survival from the onset of symptoms was 11.9 years. By contrast, those without symptoms (37 of the 280) did not differ from a control group without the disease (matched for age and sex) in survival time. The presence of jaundice, weight loss, enlargement of the liver or spleen, or abdominal fluid accumulation (ascites) each signified a poor prognosis. Survival also correlated with the stage or degree of extensiveness of the disease as determined by examination of tissue samples. Fibrosis (growth of connective tissue, as found in early scarring), if limited to a separate portal vein and bile duct area draining the liver, was compatible with long survival, while fibrosis extending from one such area to the next was not. The scarring of full cirrhosis had the poorest outlook. Similarly, the more backup of bile in the liver or destruction of tissue in the portal vein area, the worse the outlook.

Finally, a statistical analysis showed that poor survival time could be predicted at the first onset of symptoms from the age of the patient, the size of the liver, or an increased level of bile pigment (bilirubin) in the blood serum.

Research Directions

Clinical application of these findings to trial groups of patients is desirable, to identify those subgroups with poorer chance of long-term survival. Such subgroups can be given more intensive attention; the use of methods of treatment that carry more risk to the patient, such as the drug D-penicillamine, is warranted when the risk of poor survival is greater. These criteria

are valuable in selecting patients for liver transplantation. Developing and perfecting new treatment alternatives must be accompanied by defining the conditions of their clinical application—which in turn depends upon considerations of relative risk and effectiveness determined from clinical trials.

Metabolic Error of Cholesterol Metabolism

Prior Findings

A metabolite of cholesterol, the 26-hydroxy derivative, is also a powerful inhibitor of cholesterol synthesis (in cell culture, in concentrations no greater than those that exist in normal plasma) and may play some regulatory role in cholesterol synthesis or deposition in tissues. This metabolite was thought earlier to be formed only during fetal and neonatal life, but has now been detected in normal adult plasma and, in fact, appears to be formed as an intermediary preceding the formation of the bile acids from cholesterol. This work, as well as the advance described below, was done by an NIADDK grantee.

Recent Advances

In a rare disease called cerebrotendinous xanthomatosis (CTX), the blood level of 26-hydroxycholesterol was found to be less than one-tenth normal. On this basis, a new diagnostic test specific for the disease was developed, and the underlying mechanism for the disease elucidated. Lacking the enzyme to metabolize cholesterol to its 26-hydroxy derivative, individuals with CTX have massive deposits of cholesterol and cholesterol-like substances in their arteries. This abnormal deposition occurs in spite of normal to low serum cholesterol levels, in contrast to the types of deposition found in typical atherosclerosis (associated with elevated blood cholesterol levels). Children with the disease may show neurologic problems (from blockages of blood supply to the nervous system or from an abnormal myelin layer insulating the nerves) before other symptoms develop. Detection of the defect in CTX used isotope dilution-mass spectrometry, a new analytical method for the cholesterol metabolite.

Research Directions

The method for detection of 26-hydroxycholesterol developed under this research may be adaptable as a screening procedure for CTX among children with neurologic problems. This, in turn, may lead to ways of preventing the further expression of the disease and, ultimately, to ways of correcting the genetic defect.

Dissolving Cholesterol Gallstones Safely and Effectively

Prior Findings

Removal of the gallbladder as a treatment for gallstones is associated with the usual risks of abdominal surgery plus a higher-than-usual incidence of complications. Some studies have suggested that cholecystectomy may increase the risk of cancer of the colon, as well.

Among the chemical substances used for dissolving gallstones without surgery are two derivatives of bile acids: ursodeoxycholic acid and chenodeoxycholic acid. These are isomers (having the same molecular structure but different arrangement and properties), but the first seems to be more resistant to bacterial attack in the body.

The first demonstration that chenodeoxycholic acid (chenodiol) could result in the dissolution of cholesterol gallstones met with an immediate wave of enthusiasm that led to the therapeutic use of the drug in Europe before its long-term safety and effectiveness were established. The National Cooperative Gallstone Study, supported for the past several years by NIADDK, was initiated in 1973 (following animal toxicity testing) to provide these critical data. Results of that study showed that the drug administered orally at 750 mg/day completely dissolved gallstones in 14 percent of patients within the 2-year period and partially or completely dissolved them in 41 percent of patients. Low-dose administration of chenodiol (375 mg/day) led to complete stone dissolution in 5 percent of patients and partial or complete dissolution in 24 percent. Significant side effects included reversible liver damage, usually mild diarrhea, and slightly elevated serum cholesterol.

These problems rarely have been found during treatment with ursodeoxycholic acid, which has emerged as the leading candidate for a safe and efficient chemical agent. The question assumes added importance in view of the fact that 16 to 20 million people in the United States have cholesterol gallstones.*

Recent Advances

A study under NIADDK support tested the effectiveness of three dosages of ursodeoxycholic acid in dissolving cholesterol gallstones, as well as its effects on the liver and elsewhere. The results showed that at a dose between 250 and 1,000 milligrams per day, the compound is both safe and effective. Overall, 42 of the 53 patients achieved partial dissolution of gallstones, and 27 of these were classified as complete dissolution. The drug was given orally, to patients with

* American College of Surgeons.

functioning gallbladders, for 6 to 38 months. Most biliary symptoms seemed to disappear within 3 months, and no patient developed diarrhea. There was no evidence of liver damage or other undesirable side effects. Two-thirds of the complete dissolutions took place in the first year, and all but one, by 2 years. High-dose therapy shortened treatment time for those with small stones, but in general, all dose levels were equally effective. Increased gallstone size and numbers were found to hinder the dissolution process.

This method of treatment, while safe and effective, is not a permanent cure; gallstones can recur. According to one report, as many as 50 percent of patients may have a recurrence within 7-1/2 years.

Research Directions

To prevent the reformation of gallstones after dissolution, it will be necessary to design and test some type of maintenance treatment. This treatment could take the form of regular use of the same substance used in dissolution at low dosage and at intervals to be established. Of course, the search for other substances and for other alternatives to surgery should continue.

Liver Transplantation

Prior Findings

The first effort to replace a human liver was made in 1963, under NIADDK support. From initial experience in four children, the use of the procedure by that same group has expanded to 296 transplants, including a recipient who then successfully gave birth to a child. The major liver diseases for which the procedure has been used are biliary atresia (congenital lack of bile duct growth), which claims the lives of 350 to 400 children each year, and various forms of liver failure in the adult (chronic active hepatitis, cirrhosis of several types, cancer arising in the liver). Each year, an estimated 4,000 to 5,000 people in the United States may need this operation.

Before 1980, the 1-year survival rate in adults undergoing the procedure was only about 27 percent, both in this country and in others reporting on their experiences. Many modifications of the "double drug" immunosuppression treatment using azathioprine and prednisone were tried, in combination with such adjuncts as antilymphocyte globulin (antibody against lymphocytes), drainage of lymphocytes through the thoracic duct (the main lymphatic duct), and total lymphoid irradiation, to further suppress immunological reaction. These trials, during the period from 1963 to 1979, all yielded the same disappointing results.

Major improvements have been made in the surgical techniques for liver transplant, which have contributed to increased success with this operation. In addition, new immunosuppressive agents have been developed which appear to enhance further the success of liver transplantation. One such agent, cyclosporine, is an antilymphocytic drug that suppresses immunologic reaction against transplanted tissue. It was first described in 1976 and has been used with success since 1980 to improve survival rates in transplants of cadaver kidneys. Its use in liver transplantation met with success in experimental animals then in clinical trials, first in England and subsequently in the United States.

Recent Advances

Increased survival rates have been achieved in whole-liver transplantation due to improvements in surgical technique and to the use of cyclosporine. Using cyclosporine combined with a steroid immunosuppressive and anti-inflammatory drug (like prednisone) in low doses, the most experienced U.S. team reports a doubling of the 1-year survival in both adult and pediatric liver transplant patients, in a series of 67 operated on in the period 1980-82.

There have also been advances in solving other problems associated with liver transplantation, such as vast improvements in the reconstructive surgical procedure and in bile duct reconstruction, donor liver viability, criteria for selection of patients, diagnosis of acute rejection of the transplant, and choice of the treatment combination and dosages for most effective immunosuppression. These developments all contributed to the improved survival being obtained.

Cyclosporine acts by depressing both the blood and the tissue components of immunity, but has a preferential action against the lymphocytes (T cells) that are triggered to attack the intruding graft's antigens. Lymphocytes that are not triggered are not affected by it. The drug is not without side effects, the most serious of which is the possibility that the immunosuppression may increase the incidence of lymphomas and other tumors.

Research Directions

Further progress and successes in liver transplantation depend in part on finding more, and more effective, ways of immunosuppression and, in part, on further improvements in technique; but, to a large extent, progress depends on understanding the liver itself better.

Much basic information about the control of liver function is still unknown. The availability of increasing numbers of patients at university health centers, where multidisciplinary investigators can study these patients, will provide a major resource. Because the donor liver carries its own genetically determined processing information, and the host organs carry another set of determinants, the stage is set to explore what

governs various synthetic, secretory, and detoxication processes.

Opportunities also exist to learn a great deal about other normal and abnormal liver functions.

Nutrition

New Evidence on the Effects of Dietary Carbohydrates

Prior Findings

It has long been assumed that simple carbohydrates (sugars like glucose, sucrose, and fructose) are immediately absorbed from the intestine and cause a rapid rise in blood sugar and blood insulin, while complex carbohydrates (such as the starches in rice and potatoes) are absorbed more slowly. On this basis, diabetic people were advised to avoid simple (refined) sugars and to use complex carbohydrates.

Recent Advances

It has now been shown that the effects of dietary carbohydrates on blood sugar and insulin levels do not permit a therapeutically useful distinction between simple and complex carbohydrates, and that foods must be tested individually. For example, glucose, potatoes, and honey all cause a rapid surge in blood sugar, while rice, beans, and fructose all produce a flatter curve of blood sugar response. At the same time, other variables influence the response, such as the physical form of the food, the other components of the meal (fat and fiber both slow gastric emptying, and protein stimulates insulin release), and the amount of carbohydrate present. The plasma insulin response to different types of carbohydrates tends to parallel the plasma glucose response, although there are some differences in relative levels. Results show that a meal containing potato and gelatin produces a greater insulin response than one containing rice and corn. In a related result from the same laboratory, the plasma insulin level has been shown to be correlated highly with the production of triglycerides which make up very low-density lipoproteins, one of the major blood lipids. As was known already, diabetes itself is associated with increased triglyceride levels.

Research Directions

Much more needs to be learned about the factors responsible for the blood sugar response to dietary carbohydrates. Many foods have not been tested, and little is known about food-food interactions (although there is evidence that these occur).

The implications of the new findings for diabetes diets need to be examined further, inasmuch as some of the foods evoking low blood sugar response (and thus might appear to be desirable for consumption by diabetic patients) are also high in fat and total energy content, both of which are linked to increased diabetes prevalence in epidemiologic studies.

Vitamin D Derivatives Useful in Postmenopausal Osteoporosis Treatment

Prior Findings

The biologically active metabolites of vitamin D (25-hydroxycholecalciferol; 1,25-dihydroxycholecalciferol, and 1-alphahydroxycholecalciferol) have been isolated, identified, and chemically characterized under NIADDK support. These are currently being used for the treatment of a wide variety of metabolic bone diseases, for example, renal osteodystrophy, hypoparathyroidism, pseudohypoparathyroidism, vitamin D-resistant rickets, and most recently, osteoporosis. Furthermore, the measurement of vitamin D metabolites is being used in the diagnosis of disease. Thus, low plasma levels of 25-hydroxycholecalciferol may indicate intestinal vitamin D malabsorption, biliary secretion failure, or poor vitamin D nutrition. There can be little doubt that the study of the metabolism and function of vitamin D has had marked physiological significance.

The discovery of hydroxylated derivatives of vitamin D has led to new concepts of calcium homeostasis (balance). The liver converts the vitamin to the blood (plasma) transport form (25-hydroxycholecalciferol), and finally, the kidney converts the plasma form to the hormone (1,25-dihydroxycholecalciferol), which acts to express the function of the vitamin. Target tissues responsive to this active form include intestinal mucosa, bone, kidney, parathyroid gland, pancreas, pituitary gland, and others. These basic discoveries have led to renewed interest in the role of vitamin D in calcium and phosphorus transport and retention in bone, and its relationship to bone disease states, especially osteodystrophy of renal disease and osteoporosis.

The hormonal form of the vitamin is the major hormone controlling calcium absorption, and small doses of it were found by NIADDK grantees to correct abnormalities of calcium absorption. These same investigators then asked whether this beneficial effect could be sustained with prolonged treatment, and if so, whether it could be applied to the treatment of osteoporosis. In this disease, the decline in anabolic sex hormones and abnormalities of bone and calcium metabolism lead to serious demineralization of bone and more frequent fractures, especially in postmenopausal women. The disease has a major and serious impact on our elderly population.

Recent Advances

Institute grantees addressed the question of osteoporosis treatment using small doses of the hormonal derivative of vitamin D, to avoid the adverse effects of therapy on renal function sometimes seen with use of higher doses. They have found that as little as 0.5 microgram of 1,25-dihydroxycholecalciferol, administered daily to postmenopausal women with osteoporosis, not only increased calcium balances, but more important, caused an increase in trabecular (inner structural) bone volume and decreased bone fracture rate. This group also found that plasma 1,25-dihydroxycholecalciferol levels fall after age 50, especially in postmenopausal women. Estradiol (a female sex hormone) treatment of postmenopausal women for months caused a 30–to 40–percent elevation in circulation levels of 1,25-dihydroxycholecalciferol and corresponding increases in intestinal calcium absorption.

Japanese scientists have completed a clinical trial using 1-alphahydroxycholecalciferol for treatment of postmenopausal osteoporosis with similar results; the 1-alphahydroxy form is readily converted into the active 1,25-dihydroxy form by the liver.

The NIADDK-supported researchers also have synthesized 24,24 difluoro-1,25-dihydroxycholecalciferol and found the difluoro-substituted compound to be 10 to 100 times more active, due to longer lasting biological activity.

Research Directions

These results provide reason to hope that derivatives of vitamin D may provide an effective treatment and preventive measure for postmenopausal osteoporosis. To reach definitive conclusions about the long-term efficacy of 1,25-dihydroxyvitamin D, further studies in a larger number of patients should now be undertaken. Specific attention should be devoted to the spinal column and to the incidence of vertebral fractures during treatment, to make certain that the increase in trabecular bone is not at the expense of the outer (cortex) layer of bone, which would weaken the affected vertebrae.

Either a selective calcium malabsorption or a metabolic defect on the bone level, which may be conditioned by the diminished anabolic sex hormone levels of advanced age and which is responsive to the hormonal form of vitamin D, appears to be a specific characteristic of osteoporosis. Further study of this relationship should lead to fuller understanding of the mechanisms producing this disease and to other ways of modifying the disease process.

Development of the difluoro derivative of the hormonal form, for evaluation of its safety and possible clinical use, should be pursued.

It is expected that a Japanese firm will manufacture 1-alphahydroxycholecalciferol for widespread use for treatment of osteoporosis in Japan.

Vitamin A Deficiency: A Rapid Test

Prior Findings

The earliest clinical manifestation of a vitamin A deficiency is a decrease in dark adaptation ability, or night blindness. Early detection of a deficiency and institution of prophylactic therapy could dramatically reduce the prevalence of xerophthalmia (severe dryness of the conjunctiva) and subsequent vitamin A-deficiency blindness among populations at risk. Vitamin A deficiency is a major cause of preventable blindness, contributing to 20,000 to 100,000 new cases annually throughout the world.

The classical dark adaptation test is a tedious, lengthy (45 minutes) procedure requiring cumbersome and expensive instrumentation, making it unsuitable for use under field conditions. Serum levels of vitamin A vary over a wide range in subjects with functional deficiency and thus have little predictive accuracy in identifying subclinical deficiency states.

A rapid method requiring a minimum of transportable equipment for testing dark adaptation has recently been described; while it was suitable for evaluation of retinal rod function (that is, for evaluation of light/dark discrimination without the use of color; color requires the separate retinal cells known as cones), certain inconsistencies were noted when compared to results obtained with classical dark adaptation testing (on a Goldman Weekers dark adaptometer).

Recent Advances

Under NIADDK support, a rapid test of dark adaptation, suitable for use under field conditions, has been developed as a functional measurement of vitamin A deficiency. The major change introduced involved matching the color disks used in the test to cones, that is, the intensities of the disks were matched to cone function (not to rod function) so that under dim light conditions, where cones cannot discriminate color, the ability to separate the disks by brightness is dependent on rod function. (It is based on a shift of retinal wavelength sensitivity as the eye dark-adapts, so that blue appears brighter than red when rods begin to activate under darkened-lighting conditions.) The subject separates sequentially the white, then blue, disks from a pile of red, white, and blue disks. The procedure is timed until 100 percent accuracy of sorting is achieved.

Evaluation of this modified test of dark adaptation in 32 healthy subjects and 25 patients, 14 of whom were

vitamin A deficient, revealed a sensitivity of 95 percent and a specificity of 91 percent. This test takes less than 6 minutes to complete and has been used satisfactorily with children ranging in age from 4 to 13 years, under field conditions in Guatemala and Baltimore. The mean time required for the test was 2.8 minutes.

Zinc deficiency also may delay dark adaptation, presumably due to impairment in the zinc-dependent vitamin A mobilization from the liver and transport to the retina. Zinc supplementation has been found to correct impaired dark adaptation in adults not responsive to vitamin A therapy, suggesting that this method might be useful in identifying zinc deficiency as well.

Research Directions

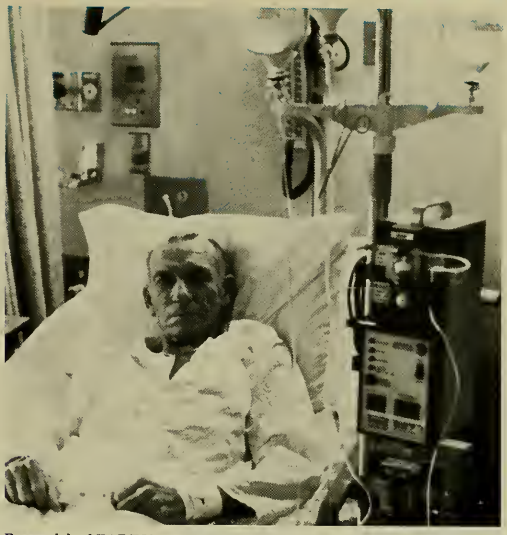
With a simplified rapid test of dark adaptation as described and validated, quantitative determination of rod function can become accessible to wider clinical use. For example, this test also can be used as a diagnostic tool for identifying other conditions in which rod function in the retina is impaired. Further work is desirable on the relative sensitivities, as indicators of early vitamin deficiency, of dark adaptation, retinol-binding-protein blood levels, and hepatic vitamin-A levels.

Mineral Needs in Intravenous Hospital Feeding

Prior Findings

Total parenteral nutrition (TPN) is a special means of providing certain patients with the proper amounts of the essential nutrients by intravenous administration, for the maintenance of health or life. TPN may be required for extensive periods in patients with malabsorption from the intestinal tract, after extensive gastrointestinal surgery, or in states of abnormally increased metabolism continuing for a considerable time such as after extensive burns. In a patient unable to ingest, digest, or absorb nutrients and not fed parenterally, starvation results in negative nitrogen balance and rapid wasting of both muscle and viscera, ultimately leading to dysfunction of the liver, muscle, and immune system. Loss of 35 to 40 percent of lean body mass during such an illness (or postoperative state) usually results in death.

Much progress has been made during the past decade in the development of TPN mixtures and systems that provide appropriate levels of calories, amino acids, vitamins, electrolytes, and trace minerals; however, much remains unknown about the rate of depletion of essential trace minerals and levels of these minerals needed by patients maintained on TPN for indefinite periods.



Research by NIADDK investigators continues on ways to improve the composition of total parenteral nutrition (TPN) solutions, by incorporating the appropriate amounts of essential trace minerals. TPN *maintains* patients who temporarily or permanently cannot ingest, digest, or absorb nutrients.

Recent Advances

The ability to provide nutrients by parenteral means in amounts needed to maintain health of patients who cannot ingest, digest, or absorb food represents a major technological advance. TPN is extremely important in rehabilitation of critically ill or surgically stressed patients, or in other short-term conditions where food cannot be taken by mouth or tube feeding. The number of individuals requiring long-term TPN in order to live has reached approximately 1,000—and this number is doubling each year.

New information on requirements and reports of trace element deficiencies in patients fed by TPN has led to an increased awareness of the importance of providing proper levels of trace elements in TPN solutions, particularly when the parenteral route is the sole or primary source of nutrients for prolonged periods. The trace elements now recognized as essential in man, in addition to iron and iodine, include zinc, copper, chromium, and selenium. These requirements become clear as a result of the deficiencies recognized in patients on TPN. In addition, investigators have described a molybdenum deficiency in a patient on prolonged TPN therapy. Other trace minerals that may be essential nutrients for man and thus needed for long-term TPN, but for which little information is available, are manganese, vanadium, and silicon. The American Medical Association published guidelines for essential trace elements in preparations for parenteral use in 1979 and has recently convened specialists to update these guidelines.

Research Directions

Recent studies underscore the importance of adequate nutritional support for patients hospitalized with chronic or acute diseases or for surgery. There are opportunities for the development of improved methods to assess nutritional status and for the acquisition of more complete information about the effects of disease states on the nutritional needs of patients. Additional attention should be given to nutritional support of the patient, to the effect of the overall nutritional status of the individual, and to the effect of nutrient intake on the course of specific diseases or conditions.

It is critically important,then, that the nutrient needs, both qualitatively and quantitatively, be determined (at least, safe ranges and proportions), to permit normal growth, development, and maintenance of health in these individuals.

Utilization of nutrients taken parenterally may be different from that of nutrients taken enterally for several reasons. The digestive tract is bypassed entirely, except for secretion into the gut, and nutrients enter the general circulation without first passing through the liver, via the portal circulation. Nutrients provided by parenteral means must be in a biologically available form. Other functions of the digestive tract caused by the presence of food or its digests in the gut, including secretion of various specific proteins, secretion of hormones, and the action of intestinal microorganisms, are lacking. Moreover, the metabolic transformations that occur in the liver are bypassed.

Studies are needed to examine the metabolic consequences of bypassing the intestinal tract and liver in TPN, especially the synthesis of nonessential nutrients and the combined nutrient-drug management of patients. Such research is greatly facilitated by the existence of the NIADDK-supported Clinical Nutrition Research Units, which have served to focus investigator attention on the nutritional needs of hospital patients.

Aluminum Toxicity in Long-Term Intravenous Feeding

Prior Findings

Several months after initiation of TPN, some patients develop metabolic bone disease (osteodystrophy). This finding suggests that the therapy itself can cause or contribute to bone disease. The same problem has been described with long-term dialysis for renal failure. Aluminum was implicated as a bone toxin in these patients, who also have low levels of parathyroid hormone. The experience with hemodialysis suggests that aluminum toxicity could be complicating the use of TPN.

Recent Advances

Increased bone aluminum was found in patients who received a common form of parenteral feeding solution, hydrolyzed casein (the main protein of cow's milk and cheese). No aluminum was found in tissue samples from normal persons, or those with parathyroid problems or (other) bone diseases. When the solutions were tested, high levels of aluminum were found in casein hydrolysate (derived from the water used in its preparation). A significant correlation was found between the aluminum level in bone and a decrease in bone formation. Even low aluminum levels were associated with reduced bone-formation rates.

Bone surfaces containing aluminum were unable to mineralize; new bone formation was inhibited; and the remaining bone was softened and lost its mineral constituents, calcium and phosphorus (osteomalacia). This toxic effect was reproduced in animal experiments. Very low levels of parathyroid hormone found in the affected patients may have been due to the low bone-formation activity, or to a direct effect of aluminum on parathyroid secretion, or both.

Patients who received amino acids instead of casein hydrolysate had an increased bone-formation rate. Removal of the aluminum from casein solutions led to improved bone formation.

Research Directions

Direct application of these findings to the prevention of bone disease symptoms and fractures caused by aluminum toxicity in long-term parenteral nutrition is possible and, indeed, essential. Careful monitoring of solutions is required. It is likely that other factors besides aluminum may be involved in the bone disease seen in some patients on TPN. Further research is needed to explore the role of abnormalities in parathyroid, vitamin D, mineral, and other metabolic factors that may occur in long-term intravenous feeding. In addition, the reversibility of aluminum toxicity needs to be explored.

Starch Blockers Fail to Limit Caloric Intake

Prior Findings

The widespread popularity of starch-blocker tablets in recent years, as diet aids, is based on their presumed ability to inhibit the action of the enzymes that digest starch (salivary and pancreatic amylase). The substance responsible for this antiamylase action is called phaseolin and is derived from plant foods such as kidney beans and wheat; it acts only on amylases from animal sources. The commercial success of the tablets preceded

any evidence that they actually reduce the absorption of calories from dietary starch in human use.

Recent Advances

Using a 1-day calorie-balance method, NIH grantees tested the effect of starch-blocker tablets with a high-starch meal (spaghetti, tomato sauce, and bread). They first washed out the gatrointestinal tract of test subjects, then fed them the meal (with a nonabsorbable marker to measure recovery), and finally measured the excretion of fecal calories—after use of either a placebo or the tablets. Instead of an increase in excreted calories after use of the tablets, there was no significant difference. The tablets had no effect as blockers of amylase digestion of starch. (It could be that enough amylase was being secreted by the pancreas to result in excess active amylase, more than the inhibitor could bind and inactivate, or there could be other types of amylase present that were unaffected by the phaseolin, or perhaps this glycoprotein itself was digested.)

The Metabolic Role of Selenium

Prior Findings

Selenium is an essential trace element known to be a component of some of the body's proteins. It appears to be effective in the prevention of certain types of cancer, in animal-model studies. It is involved in the oxidative metabolism of the body by its role in the structure of glutathione peroxidase (an enzyme controlling oxidative breakdown of membrane lipids and other tissue components and associated with vitamin E action in muscle tissue). A deficiency of selenium may lead to heart muscle pathology and disorders of heart rhythm. This information indicates that selenium has an important role in the body, but little is known beyond this.

Recent Advances

Investigators receiving NIADDK support for work on selenium have made a series of advances: (1) the amino acid sequence at the site of enzymatic action was determined for glutathione peroxidase, showing that the selenium it contains is present in fixed combination with the amino acid cysteine, in the "backbone" of the enzyme molecule, (2) amino acid analyses of other selenium-containing proteins were made, showing the presence of the same combination (selenocysteine) in all, and (3) the complete metabolic machinery necessary for the production and assembly of new molecules of selenocysteine, through the conventional nucleic acid (DNA-RNA) pathway, has been identified. The discovery of a transport form of RNA (tRNA) linked to selenocysteine (via an aminoacyl linkage) means that this mechanism is normal in protein synthesis. The selenocysteyl tRNA exhibited the specificity and other qualities required in the pathway of synthesis of selenoproteins.

Research Directions

More rapid progress should now be possible in the area of selenium metabolism and its applications to muscle function, to cardiac arrhythmias, and possibly even to the prevention of cancer. Its role in the mechanism of enzyme activity should now be examined, and further details of the synthesis and structure-activity relationships in selenium-containing proteins should be sought. The full range of biological functions and actions of selenium needs to be elucidated.

A New Method for Estimating Total Body Fat and Lean Tissue

Prior Findings

A method based on a new principle has been developed to estimate the amount of lean tissue in the body as compared with total body fat. Because lean tissue has a much higher electrolyte content (sodium and potassium ions, for example), its electrical conductivity is far greater than that of fat. This conductivity shows up as the change in an oscillating radiofrequency current (change in coil impedance) when the body is placed in an electromagnetic field; the change is proportional to the total electrical conductivity of the body and, therefore, to the lean body mass (LBM). The total body fat is obtained by subtracting the LBM from the total body weight.

This method has been used in the meat industry and was validated in pigs by dissection and weighing of the lean and fat components and by a body potassium assay.

Recent Advances

A team of NIADDK grantees has adapted the method for total body electrical conductivity (TOBEC method) to human use and has provided a safe, simple, rapid, and convenient way to assess nutritional status. A large coil was designed to accommodate the human body, allowing the individual (adult) subject, supine on a stretcher, to be rolled into the instrument. In one experiment of this method, four readings were taken over a 10-minute period for each of 19 subjects, and the mean of the four readings was compared with other data on the same subjects derived from body measurements (anthropometry), an isotope (tritium) dilution method for total body water, and a total body potassium measurement. The agreement of the new

TOBEC method with these last two measures was excellent, and its agreement with the values for lean body mass calculated from anthropometry was very good, but less strong. Fat stored in adipose tissue does not affect the TOBEC readings for lean body mass, but shows up as calculated fat when the lean mass is subtracted from total body weight.

Research Directions

Further experience with the use of the TOBEC method under different conditions (such as the state of hydration) and with different types of subjects is needed, as is validation by comparative studies of subjects measured by a variety of methods and measurements taken on standardized representations of the body (phantoms). Because the method is noninvasive and rapid, it should be adapted to the screening of special populations for nutritional status and body composition.

Special Programs

National Digestive Diseases Education and Information Clearinghouse

As a major information service of the NIADDK, the National Digestive Diseases Education and Information Clearinghouse coordinates the national effort to educate the public, patients, patients' families, physicians, and other health-care providers about the prevention and management of disgestive diseases. The program is specially designed to reach neglected population groups, such as the elderly, minority groups, rural Americans, and children.

The clearinghouse provides a central point for the exchange of information among professional organizations, foundations, and voluntary health organizations involved with digestive health and disease. In working with these groups, the clearinghouse aids in the distribution of information products, determines what additional materials are needed, and encourages production of such materials.

Fact sheets produced by the clearinghouse describe specific disease areas and are prepared by professionals in the field at the request of the clearinghouse advisory subgroup. Another clearinghouse publication, "Letter from the Clearinghouse," discusses current research and the activities of various government and private-sector organizations. The clearinghouse has collaborated with organizations of laymen in distributing to their chapters nationwide the fact sheets, a flyer describing the clearinghouse, a glossary of digestive diseases terms, and a directory of organizations concerned with digestive diseases.

Clinical Nutrition Research Units

Research in human nutrition is truly interdisciplinary and complex, being dependent on the close interactions of several basic research disciplines for breakthroughs in fundamental knowledge and on the appropriate medical specialties for rapid integration into clinical studies. In a joint effort with the National Cancer Institute, the NIADDK has fostered the development and operation of Clinical Nutrition Research Units (CNRU's) to encourage a multidisciplinary approach to clinical nutrition research opportunities and problems. Core grants awarded through the program are designed to provide support for common laboratories and a focus for clinical nutrition research and related educational and service activities in biomedical institutions and to complement ongoing research project grants and training awards. In addition to providing an enhanced environment for the education of medical students, residents, practicing physicians, and trainees and fellows in nutrition, each CNRU also provides support for a new investigator in clinical nutrition.

Currently there are seven CNRU's in operation, five of which are funded by the NIADDK. The CNRU awards have been conspicuous in stimulating progress in multidisciplinary research in clinical nutrition, enhancing patient care, strengthening training environments, and generating nutrition information for the public.

Program Accomplishments

Activities pursued by the Division staff in the recent past include the development of diagnostic criteria for functional bowel disease (disease of abnormal functioning, usually having a strong psychological component); a cooperative study of the prevalence of gallstones in Hispanic Americans, with the National Center for Health Statistics; the development of an epidemiology and data systems program for digestive diseases within the NIADDK; and the preparation of a data system allowing retrieval of information on the research activities of all NIH Institutes, and of other agencies, concerned with digestive diseases. In addition to the items discussed below, specific accomplishments have included the following: (1) guidelines were developed, and a request for applications was issued, for exploratory grants for digestive diseases core centers, in February 1983, and (2) a sources-sought announcement was issued to identify organizations eligible to compete for grant support under a program to create, and develop through research, remote spectrometry technology and devices for use with the fiberoptic endoscope.

Consensus Development Conference on Liver Transplantation

Since performance of the first human orthotopic liver transplantation in 1963, over 540 such operations have been carried out in four medical centers in the United States and Western Europe. Additional liver transplantation procedures have been performed in other parts of the world and, more recently, in several other American medical centers. Many issues concerning liver transplantation are still unresolved. Graft rejection remains a significant problem, as do methods for obtaining appropriate donor livers in a timely fashion. The prognosis for quality of life and long-term survival after liver transplantation, under current management capabilities, is still open to question. Overall long-range benefits and risks of transplantation in specific liver diseases need to be determined.

In June 1983, the NIADDK sponsored a consensus conference on liver transplantation, bringing together leading hepatologists, transplant surgeons, internists, pediatricians, a medical ethicist, and a public representative to address the following questions: (1) Are there groups of patients for whom transplantation of the liver should be considered appropriate therapy? (2) What is the outcome (current survival rates, complications) in the above groups? (3) In a potential candidate for transplantation, what are the principles guiding selection of the appropriate time for surgery? (4) What are the skills, resources, and institutional support needed for liver transplantation? (5) What are the directions for future research?

In formulating their answers to these questions, the panel concluded that the procedure has merit, especially because many people would die without it, but cautioned that "The interpretation of existing data on survival is extremely difficult because no control data are given for comparison, surgical techniques and drug therapies varied over time, and patient selection criteria and management differed across centers." The panel urged that additional data on the procedure be collected and evaluated. For liver transplantation to gain its full therapeutic potential, the indications for and results of the procedure must be the object of comprehensive, coordinated, and ongoing evaluation in the years ahead. This evaluation can best be achieved by expansion of this technology to a limited number of centers where liver transplantation can be carried out under optimal conditions.

Workshop on the Epidemiology of Inflammatory Bowel Disease

This workshop was designed to review existing information on the epidemiology of inflammatory bowel disease and then to identify areas for future research in epidemiology. The recommendations emerging from this workshop included: establish an international committee to set diagnostic criteria, clinical as well as pathological, with field testing, and seek agreement among experts on the criteria; establish an inflammatory bowel disease data group; standardize diagnostic procedures; observe the natural history of the disease and look for clues to the etiology and pathophysiology, and identify prognostic factors; determine the full extent of the disease, as opposed to solely those cases that are clinically obvious; and establish a case registry, if feasible.

Workshop on Anorectal Disease Research Opportunities

Anorectal diseases and disorders represent a major national problem in terms of morbidity and detraction from quality of life. Diseases and disorders covered in the workshop organized by the NIADDK included hemorrhoids, fissures, fistulas, rectal prolapse, constipation, anorectal pain, and fecal incontinence.

This workshop was the first to be convened at NIH to address planning for research and research training for anorectal diseases and disorders (exclusive of cancer and infectious diseases).

The products of the workshop included: a program announcement on research in anorectal diseases, revised and endorsed by the participants, for publication in the *NIH Guide for Grants and Contracts;* detailed plans for planning workshops on specific topics in anorectal diseases, disorders, and related basic sciences; advice on priorities for implementation of planning recommendations; advice on needs, opportunities, and strategies for training of researchers in both basic and clinical studies on the anorectum; and identification of societies and other professional and lay organizations with which the NIADDK should relate in planning and information exchange in anorectal research and research training.

Workshop on Chronobiology

An earlier conference, organized and sponsored by the NIADDK with the assistance of the University of Minnesota, examined the work that has been done on time-dependent periodic changes in the digestive system and suggested areas of needed research on the digestive system in which the time factor must be considered. Attendees included many international authorities on chronobiology whose work has impinged entirely or partially on the study of gastrointestinal function and pathology.

An important followup to this meeting was a second workshop held at the NIH in March 1983, with the assistance of the National Digestive Diseases Education and Information Clearinghouse. The program was designed to provide basic information to gastroen-

terological researchers on how to introduce chronobiologic methods into their research. Several prominent investigators who attended the meeting felt that the subject matter was important to the field and suggested that it would be important to conduct a tutorial type of program at the next meeting of the American Gastroenterological Association, so that additional investigators might be exposed to this area of experimental design and data analysis.

Decision Analysis Workshop

The National Commission on Digestive Diseases has pointed out the need for the application of decision theory to problems in digestive diseases having a bearing on selection of tests, selection of treatments, minimization of cost, and risk to patients. It also recommended that algorithms be developed for the management of important problems in digestive diseases. (An algorithm is a formalized model for procedure analysis and decision points.) The National Digestive Diseases Advisory Board (NDDAB), through its committee on patient care, has commissioned the development of an algorithm for the management of patients at high risk for cancer of the colon. This algorithm provides examples of the application of decision theory.

The NIADDK, in accordance with the recommendations of the commission, intends to hold a workshop on the application of decision theory to digestive disease problems and has held a planning meeting, which included experts in decision theory and in digestive diseases. The use of decision theory as envisioned by the commission should be helpful to improving the quality and value of clinical research in digestive diseases.

Nutrition Workshops

In the past year, the Nutrition Program has:

- Convened a planning workshop on Nutrition Research Opportunities in Long-Term Total Parenteral Nutrition (TPN), which will lead to a series of focused workshops on the metabolic and pathophysiological effects induced by long-term TPN. These will include such workshops as optimizing the amino acid composition of TPN solutions, fate of intravenous lipids in TPN, and substrate/hormone regulation in long-term TPN.
- Sponsored a workshop on classification of obesities, which is expected to lead to a consensus as to the minimal list of measurements that should be recorded in any clinical obesity research.
- Sponsored a workshop on Practical Approaches to Eradication of Subclinical Iron Deficiency jointly by the United States' and Japanese Malnutrition Panels, U.S.-Japan Cooperative Medical Science Program, in Tokyo, December 7-8, 1982. It is clear that iron deficiency can have functional performance effects beyond merely resulting in anemia.
- Sponsored a Summer Research Conference on Trace Elements in Nutrition, with the Federation of American Societies for Experimental Biology.

Conferences

Conferences on research and clinical developments and advances in biomedicine facilitate the immediate exchange of information and cross-fertilization among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions. It is the fastest and most effective type of cross-fertilization process in biomedical research.

- International symposium on Isolation, Characterization, and Use of Hepatocytes, held October 22-24, 1982, at the University of Indiana.
- Workshop on Research Advances and Opportunities in Gastrointestinal Endoscopy, cosponsored by the Digestive Diseases Interagency Coordinating Committee and the American Society for Gastrointestinal Endoscopy (April 1, 1983), NIH.
- Support for Advances in Pancreatic Physiology conference, at the University of Missouri.
- Support for Workshop on Intestinal Immunity and Inflammation, of the American Gastroenterological Association.

Accomplishments of the National Digestive Diseases Education and Information Clearinghouse

Distribution of materials has been primarily through professional and lay organizations. The clearinghouse has collaborated with the lay digestive diseases organizations for distribution of material to their chapters and members. These clearinghouse education materials include the fact sheets *Cirrhosis of the Liver, Diarrhea: Infection and Other Causes, Heartburn, Gallstone Disease, Bleeding in the Digestive Tract, Milk Intolerance,* as well as a flyer, "Directory of Organizations," and the "Glossary of Digestive Disease Terms," "Notes," and the "Letter from the Clearinghouse."

Development of future fact sheets has been ongoing, with manuscripts in progress on the following topics: facts and fallacies about digestive diseases, indigestion, dietary fiber, malabsorption/maldigestion, milk protein allergy, stomach ulcers, inflammatory

bowel disease, common digestive diseases, and the general digestive system. Other topics recommended for future fact sheets are: irritable bowel syndrome, indigestion, dietary fiber, yellow baby, alcohol and digestive diseases, and smoking and digestive diseases.

A plan for evaluating patient education materials currently available was designed, and the materials within the scope of coverage by the clearinghouse have been evaluated. A listing of these approved publications was distributed.

A plan for designing a combined patient education data base, with an accompanying thesaurus, was developed by seven clearinghouses of the DHHS. The purpose of the data base is to combine references and full text of short information materials from all seven clearinghouses, enabling users of the data base to have access to information from all of them. Testing of the design is being carried out by two of the clearinghouses.

The clearinghouse participated in the launching of the National Digestive Disease Education Program with the NDDAB's subcommittee on education and with the Coalition of Digestive Disease Organizations, an organization of many of the lay and professional digestive diseases societies.

Accomplishments of the Clinical Nutrition Research Units

Currently the NIADDK funds five CNRU's at different medical centers to encourage a multidisciplinary approach to clinical nutrition research opportunities and problems. Core grants awarded through the program are designed to provide support for common laboratories, a focus for clinical nutrition research and related educational and service activities in biomedical institutions, and to complement ongoing research project grants and training awards. In addition to enhancing an environment for the education of medical students, residents, practicing physicians, and trainees and fellows in nutrition, each CNRU also provides support for a new investigator in clinical nutrition.

A report on the evaluation of the CNRU's is being prepared. Emphasis on shared core laboratory facilities has proven especially valuable in increasing the number of multidisciplinary studies. An average of 32 new clinical research protocols, ranging from 22 to 39, are now active at each CNRU. Studies include the role of nutrition in diabetes, cystic fibrosis, digestive diseases, renal disease, cardiovascular disease, cancer, and care of seriously ill patients, as well as growth, aging, and metabolism. Improvements also have resulted in the coordination and delivery of nutrition-related patient care, as well as in communication of nutrition research advances to professionals and to the public. Education of medical students in clinical nutrition also has been strengthened as a result of the work of the CNRU's.

U.S.-Japan Malnutrition Panel

The NIADDK has continued to administer the U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Science Program. The research fostered under the United States' and Japanese malnutrition program is aimed primarily toward finding solutions of most benefit to the undernourished people of Asia. The most common states of undernutrition are protein-energy malnutrition and iron and vitamin A deficiencies. Superimposed are various diseased states, particularly diarrheal infections, that cause impaired utilization and loss of nutrients and constitute the primary cause of death of children under 5 years of age. Iron deficiency, which is widespread in many areas (including the United States), causes a common form of anemia and is believed to interfere with immune response, to cause lowered resistance to infection, and to reduce functional physical capabilities and possibly impair mental and learning processes. Vitamin A deficiency in turn causes many thousands of cases of damaged vision and total blindness in young children each year. A workshop on Vitamin A and Cancer is being planned for 1984.

Program Plans

Stimulation of Multidisciplinary Basic and Clinical Research in Digestive Diseases Through Initiation of a Digestive Diseases Centers Program

Many of the research areas in the various digestive diseases require a coordinated, multidisciplinary approach that can best be fostered within a center environment. Digestive diseases research centers are being planned to be based at institutions with demonstrated research excellence, i.e., a nucleus of funded investigators will coordinate and expand their efforts via a core center grant. Each center should conduct both basic and clinical research and should bring current basic science knowledge and techniques to bear upon clinically relevant digestive diseases. There will be solicitations for all areas considered to fall within digestive diseases, but some areas especially in need of a center are inflammatory bowel disease, pancreatitis, functional bowel disease, and chronic liver diseases. Such centers would serve as a stable, long-term resource for coordinating basic and clinical studies of well-defined groups of patients. The core group of investigators—such as biostatisticians, epidemiologists, molecular biologists, and immu-

nologists—could also attract the cooperative participation of practitioners and their patients from other specialties appropriate to the digestive disease under study.

The centers approach also offers a model environment for the training of specialists in the study of digestive diseases. There are currently two centers for liver diseases and one for ulcer disease.

Program Announcement: Stimulation of Research in Liver Transplantation

In the last 4 years, since the introduction of cyclosporine as an immunosuppressant in transplantation, the clinical results have improved significantly for the short-term survival of liver transplants. The increasing numbers of patients with liver transplants permit the study of important problems in metabolic liver diseases as well as basic problems such as tissue rejection and regulation of liver synthesis and secretion. Much basic information about the control of liver function is still unknown. The availability of increasing numbers of patients at university health centers, for study by multidisciplinary investigators, will provide a major resource. A consensus conference held in June 1983 on the subject of liver transplantation recommended research areas that should be pursued.

Control of Upper Gastrointestinal Bleeding: A Clinical Trial

Gastrointestinal bleeding accounts for at least 150,000 hospital admissions each year in the United States. In spite of improvements in diagnosis and supportive therapy, mortality from upper GI hemorrhage with existing treatment remains approximately 10 percent. The proportion of patients over age 60 with bleeding has increased significantly (from 8 percent in 1937 to 45 percent in 1976) and can be expected to increase further with the increase in the proportion of the elderly in our population. Older patients are at increased risk of dying from hemorrhage. The mortality from surgical treatment remains unacceptably high in these patients.

It is usually possible to visualize the site of bleeding with an endoscope. During the past 5 years, research and development efforts have resulted in a number of hemostatic modalities that could be used in conjunction with the fiberoptic flexible endoscope. These measures include laser photocoagulation, tissue adhesives, thermal probe, and three modes of electrocautery using monopolar, bipolar, and multipolar electrodes. Laboratory and clinical studies have attempted to evaluate the efficacy and safety of these procedures. Noncontrolled pilot trials have demonstrated the potential value of some of these modalities. Laser photocoagulation and electrocautery are being used now in the clinical setting, without adequate proof of efficacy and safety for the patient. To date, a multicenter, controlled clinical trial has not been performed; however, there are sufficient data regarding laser and electrocautery to warrant proceeding to such a trial. When factors other than safety (risk) and efficacy are considered such as cost, installation, and maintenance requirements and mobility, it is not practical to include laser therapy. The bipolar and multipolar probes hold the greatest promise for treatment of upper gastrointestinal hemorrhage.

The American Gastroenterological Association and the American Society for Gastrointestinal Endoscopy jointly supported a workgroup to develop a proposal for a clinical trial. This was submitted as a research grant proposal in March 1981 and later withdrawn. Currently, the Institute stands ready to send out a request for proposals for a clinical trial in this area.

Application of Endoscope Technology to Digestive Diseases

Endoscopy has made it possible to look inside the digestive tract and to obtain secretions directly from the pancreatic and biliary ducts. The advantages to be obtained from this technology have been recognized and utilized in diagnosis and treatment of digestive diseases; they have not, however, been used for research. It should be possible to look at and actually magnify the mucosa of the stomach, intestine, and duct system, to stain and identify mucosa on the basis of selective staining. It is also possible to obtain pure secretions from the pancreas and biliary tree.

To explore these opportunities, gastroenterologists, basic scientists, and engineers were invited to a conference in 1982 concerning the possible application of endoscopic technology to the study of gastrointestinal mucosa and gastrointestinal secretions. At that meeting, intramural scientists from the Biomedical Engineering and Instrumentation Branch of the NIH Division of Research Services described two devices that would facilitate study. The first is the toposcopic catheter, which can be propelled, by fluid injection into its lumen, through tortuous vessels and ducts that are not accessible to a normal catheter. (This device was originally developed for catheterization of blood vessels.)

The second device is a fiberoptic probe, which is approximately 0.5 mm in diameter, that can be introduced through the catheter to provide continuous readings of acidity (pH). This device uses two fiberoptic strands attached to a matrix in which an indicator is imbedded. Light sent down through one strand passes through the matrix and indicator, reflects off a mirror, and returns through the second strand. The inventors

suggested that virtually any indicator could be imbedded in the tip of such a fiberoptic bundle, and thus, parameters that can be measured by dye techniques could be studied continuously. Accordingly, the changes in a parameter could be observed under physiologic conditions and in response to drugs.

The expansion of the program is predicated on the demonstration that the toposcopic catheter can be used in studies of the digestive tract, including the biliary tree and pancreatic duct. This testing is under way and is being conducted by scientists and clinicians of the NIADDK and others, including the inventing engineers in the Division of Research Services. If tests are successful, a program of support of individual research grants in this area will be announced.

Meeting Research Needs in Pancreatitis

Pancreatitis is a general term that designates a group of diseases in which the basic lesions are injury of acinar cells (the acinus is the glandular secretory unit) and inflammation of the pancreas. Although we know a number of clinical settings that are associated with, and a number of conditions thought to cause, pancreatitis, we know almost nothing about its pathogenesis (mechanism of development). Biopsy of the pancreas has long been regarded as a dangerous procedure. The ability to obtain safe and convenient biopsy samples of the pancreas would allow techniques from various disciplines to be applied to the analysis and characterization of the changes in the pancreas that accompany the onset and propagation of the various disease states. Many animal models of pancreatitis have been reported; however, the usefulness of information derived from studies of the animal models has been limited by our ignorance of the extent to which the disease process in animals resembles pancreatitis in humans. Better understanding of the pathogenesis of human pancreatitis should facilitate development of meaningful animal models. Other types of systems that could be explored for their potential of being used to establish models of human pancreatic diseases are tissue and organ culture, for maintenance of pancreatic tissue. Proposed is support of multidisciplinary research focusing on basic studies of the mechanisms of inflammation, the development of techniques to obtain pancreatic tissue from patients with pancreatitis, the elucidation of the pathogenesis of the various types of human pancreatitis, and the development of meaningful experimental models of the various diseases constituting human pancreatitis.

It has been recommended that either two specialized centers of research or two research program projects be funded in the area of pancreatitis.

Program Announcement: Research on Interactions Within the Pancreas

The pancreas contains two basic types of glands: those that secrete a fluid rich in digestive enzymes and hormone-like substances through the pancreatic duct into the intestine, called exocrine glands, and those that secrete the hormones insulin, glucagon, pancreatic polypeptide, and somatostatin into the blood, called endocrine glands. Islets of endocrine tissue are scattered between the exocrine acini (glandular cell units) in man, other mammals, birds, and reptiles. Attention is now beginning to focus on interactions between the exocrine and the endocrine regions of the pancreas, under both physiologic and pathologic conditions.

Studies reveal both cell-to-cell contact between these two types of tissue and direct connections between the capillaries of the islets and the acini. Scientists have suggested that these structural arrangements reflect a regulatory role of the islet hormones in the function of the exocrine pancreas. Recent evidence indicates that, of these hormones, insulin directly and indirectly influences the function of pancreatic acinar cells. A program announcement is planned to encourage applications for funding of relevant research projects.

Program Announcement: Interdisciplinary Research on Pigment Gallstones

New information has suggested the classification of pigment stones into two major types: the calcium bilirubinate stones (subtypes brown and black) and the inorganic or organic calcium salts stones. Epidemiologic data suggest that the black pigment stone regularly accounts for about 20 to 30 percent of gallstones in the United States. In Japan, by comparison, there was a high incidence of brown stones (60 percent), which has decreased over the last 40 years (to 24 percent), whereas that of black stones increased (from 0 to 7 percent). These changes have been attributed to the introduction of a Western diet high in protein and refined carbohydrate. There are numerous areas for future research in pigment gallstone disease such as: defining risk factors in various populations by controlled epidemiological studies; learning the structural and chemical composition of stones; defining the bilirubin structure in aqueous solutions; examining the interactions of calcium, bile salts, protein, and biliary lipids with bilirubin in native and model bile solutions; elucidating the roles of stasis and infection in the formation of brown pigment stones and defining the abnormality in bile surrounding black pigment stones; and using animal models to provide mechanisms of stone formation.

A program announcement will be prepared, inviting collaborative efforts addressing the above questions,

involving teams composed of epidemiologists, physical chemists, organic chemists, basic scientists, and clinicians.

Program Announcement: Research on Infectious Diarrhea

Diarrhea from infectious causes still contributes considerably to neonatal and infant morbidity and mortality in much of the world; moreover, acute diarrheal disease is a major cause for sick leave and loss of productivity, even in Western societies. Chronic diarrheal diseases, including diarrhea due to intestinal malabsorption, although less common, are important because of their long-term morbidity in the young. Causative bacteria, viruses, and parasites have been recognized, but additional infectious agents await identification. It has recently become clear some of the infectious diseases of the gastrointestinal tract are mediated by attachment of microorganisms to the intestinal mucosal surface of the host. Such attachment, or adherence, of microorganisms promotes colonization of the gastrointestinal tract. The attached organisms retain the ability to divide at the surface while resisting being washed away by secretions produced all along the digestive tract and by the normal peristaltic movements of the intestines. Evidence suggests that, in each case, mucosal adherence is mediated by a specific binding site-receptor site interaction between surface structures elaborated by bacteria and naturally occurring elements of the host mucosal surface, respectively. Rapid progress has been made in localizing the colonization factor antigens (adhesins) of bacteria to a class of hairlike appendages termed "pili" or fimbriae. In a number of cases these structures have been isolated, purified, and characterized immunologically and biochemically. The pili from different organisms are often antigenically distinct. Research on pili may provide the basis for developing vaccines against a number of human and animal diseases for which none currently exist. The goal of vaccine research is to elicit production of antibodies against the pili and thus prevent the attachment to cell surfaces of bacteria bearing the projections. Vaccines consisting of pili are now being tested in human volunteers for immunization against gonorrhea and against *E. coli*-induced diarrhea. In addition, vaccines to protect newborn calves and pigs against diarrheal diseases are already marketed in Canada and Europe.

Progress has been made in defining the specific receptors on the gastrointestinal surface of the host that mediate adherence. For example, a receptor for cholera toxin has been identified. Proposed is support of multidisciplinary research on the structure, specificity, and role in enterotoxin and microbial binding of the carbohydrate and other potential recognition systems of the host receptor sites. These studies would very likely serve as a basis for developing a rationale for therapeutic intervention in diarrheas from infectious causes. Thus, protection against these diseases may be possible by developing appropriate mucosal surface receptor site analogues to either present colonization or dislodge the causative microorganisms from the intestinal mucosal surface of the host.

Stimulation of Research on Anorectal Disorders

Anorectal diseases and disorders represent a major national problem in terms of morbidity. Those represented in this initiative include hemorrhoids, fissures, fistulas, proctitis, rectal prolapse, constipation (in part), and fecal incontinence. In contrast to the national significance of anorectal health problems, this field has always been markedly underrepresented in medical school training of physicians and in NIH research and research training support.

For treatment of hemorrhoids alone, there are over 2.5 million patient-physician visits each year, resulting in about 240,000 hemorrhoidectomies, requiring hospitalization.* Data on hemorrhoids, as on other anorectal disorders, are not current. The prevalence in 1972 of hemorrhoids in the United States was about 10 million, and the annual incidence was about 1 million.* These figures have probably continued upward with increases in the adult (and aged adult) population.

Epidemiologic data on anorectal diseases and disorders are limited. Diagnostic criteria are often inadequate. For example, problems attributed to hemorrhoids are frequently not due to hemorrhoids. A tendency for the public to attribute all anal problems to hemorrhoids leads to a likelihood of postponing needed evaluation. Overall, there is a marked ignorance of anorectal disorders, on the part of both the public and the general physician.

Other than research on neoplasms and, to a lesser extent, on infectious diseases, there is little NIH research support in anorectal disorders. Program announcements will be issued, and collaboration with other NIH Institutes will be sought.

Research on Oral and Parenteral Nutritional Requirements

At present, approximately 1,000 people of various ages are being maintained on long-term TPN, and the number is doubling each year. The nutritional needs of most of these individuals must be met entirely by the TPN mixtures used. It is critically important for these patients that the range of levels and proportions of biochemical substances needed for normal cell functions is

* American College of Surgeons.

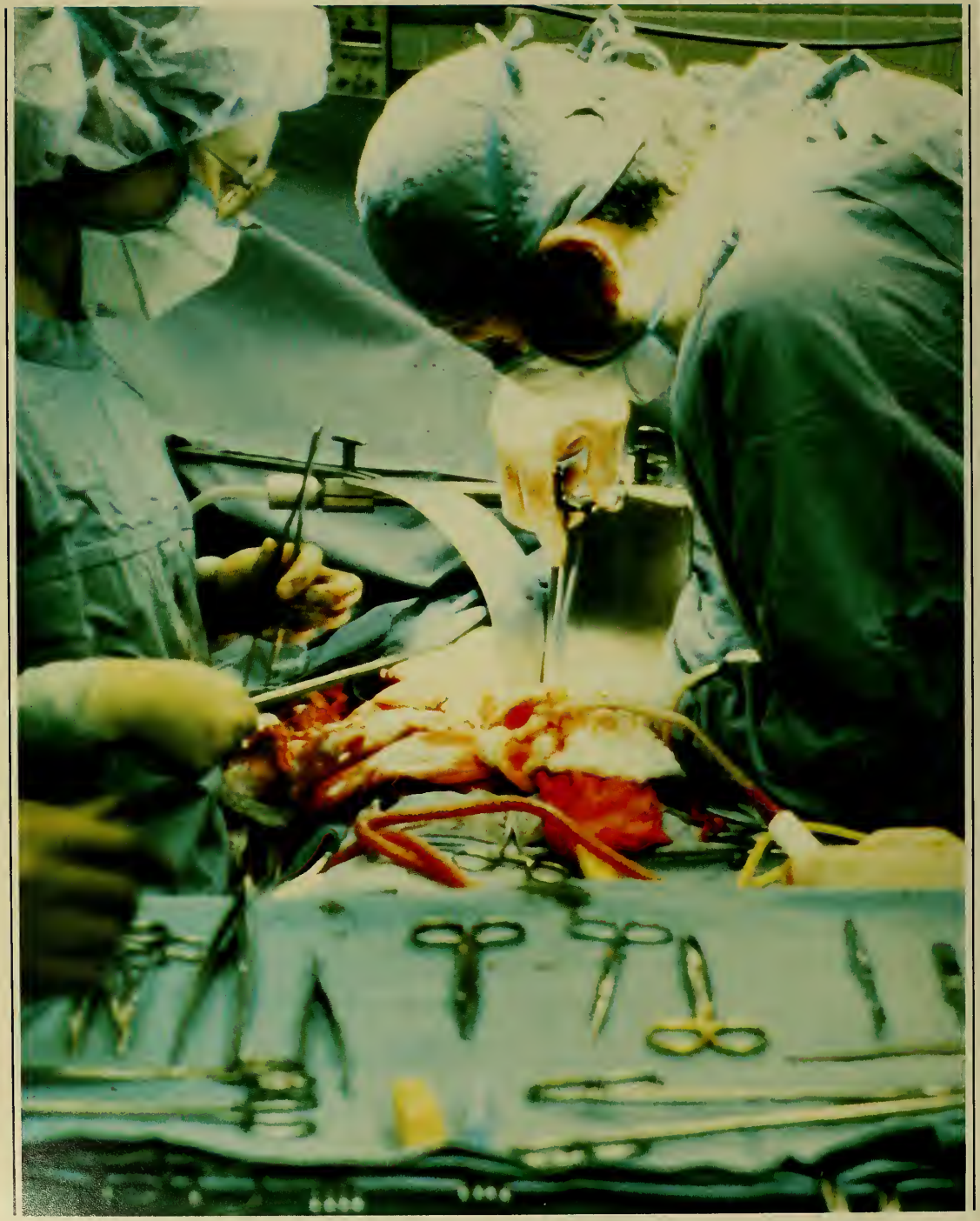
known, so it can be provided. Individuals who are entirely dependent on TPN mixtures for long-term sustenance offer a unique opportunity to determine quantitative and qualitative aspects of requirements of humans for available nutrients.

The research to be supported under a future program announcement should obtain more complete information about human dietary requirements (and safe levels) for nutrients and factors that influence these requirements. Immediate research goals are to determine the range of safe levels for those nutrients that are most likely to be provided in inadequate or toxic amounts or that may be affected by drugs or nutrient imbalances. Nutrients of particular concern are the trace minerals, certain vitamins, and essential amino acids. Advantage will be taken of the unique opportunities offered by long-term TPN in determining nutritional requirements. The initial focus of this program will be on nutritional requirements of patients receiving TPN at home.

Expansion of the Clinical Nutrition Research Unit Program

Research is needed to develop improved methods of nutritional status assessment and more complete information about the nutritional needs of patients.

The CNRU's are already upgrading the role of clinical nutrition in the institutions involved. If this program could be expanded, it would greatly strengthen the perception by clinicians of the vital role of clinical nutrition in medicine, stimulate appreciably the development of multidisciplinary research and research training in clinical nutrition, and materially improve the nutritional support of hospital patients.



V. Research Focus—Kidney, Urologic, and Hematologic Diseases

Overview

Research efforts supported by the Division of Kidney, Urologic, and Hematologic Diseases are concentrated on the development of new methods of preventive therapy, early diagnosis, and more effective treatment through understanding of the basic mechanisms and causes of these disorders.

The kidneys are vital organs critical to maintenance of the body's internal environment, particularly the composition, volume, and pressure of the body fluids. In the Renal Physiology/Pathophysiology Program, studies address not only the normal structure and function of the kidney but also the pathogenesis of renal diseases such as glomerulonephritis, interstitial nephritis, and acute renal failure. In past years, such research has increased our knowledge of renal metabolism and the immunological causes of renal disease and has resulted in the development of several lifesaving measures.

In the Chronic Renal Disease Program, studies focus on the metabolic and systemic abnormalities of uremia, a toxic condition that develops once renal failure is sufficiently advanced. The condition affects more than 10 per 100,000 persons annually.* Other research projects are devoted to improving methods of kidney transplantation and maintenance therapies for end-stage renal disease (ESRD) patients and reducing the associated complications. Advances that have resulted from these investigations make useful lives possible for many patients who otherwise would have died after loss of kidney function. For example, hemodialysis (use of an artificial kidney machine to remove poisonous wastes directly from the blood) has been improved through new techniques; peritoneal dialysis (a procedure for clearing toxic waste across the peritoneal membrane) has become a clinically effective alternative to hemodialysis in the treatment of ESRD; and kidney transplantation has evolved from a method of last resort to the treatment of choice for certain patients.

Inseparable from the function of the kidneys is the function of the lower urinary tract, the primary concern of the Urology/Urolithiasis Program. Urinary tract infection, neuromuscular disorders of bladder function, obstruction, and kidney stone disease (urolithiasis) account for about 20 percent of deaths from kidney disease. Together, these interrelated conditions account for a major portion of all disability caused by disorders of the urinary tract and affect an estimated 8 million people in the United States each year. To provide insight into the causes and development of these multiple diseases, the NIADDK supports many basic science investigations in both normal and abnormal lower urinary tract physiology as well as clinical studies of techniques to control resulting disorders. As products of this research, new drugs have been developed that permit effective treatment of serious infections and prevent recurrence of certain types of kidney stones, and advances in urologic surgery have led to the ability to repair congenital anomalies and surgically reconstruct diseased organs.

* National Kidney Foundation.

Analytical studies of blood and blood properties supported by the Institute endeavor to develop better treatments and preventive methods for diseases such as sickle cell anemia, aplastic anemia, and Cooley's anemia.

Facing page

Kidney transplantation has become the treatment of choice for some patients with end-stage renal disease. NIADDK studies have shown that the selective use of multiple pretransplant blood transfusions and of immunosuppressive agents such as cyclosporine and antilymphocyte globulin can result in marked increases in survival rates for the transplanted organ.

The Division also supports a program of hematologic research in normal blood cell function and the pathogenesis of various diseases affecting the blood cells. Five major disease categories are of particular interest: anemias of genetic origin, nutritional anemias, metabolic disorders, disorders of blood cell production, and autoimmune hematologic disease. These research studies, which are coordinated closely with other NIH blood disease programs, range from determination of the molecular structure of abnormal types of hemoglobin (the protein that enables blood cells to act as oxygen carriers) to clinical application and evaluation of new treatment methods of certain blood diseases such as aplastic anemia, Cooley's anemia, and sickle cell disease. This research has increased both fundamental and applied knowledge about blood and has led to improved management of many specific diseases.

Highlights of Research Advances

The following section briefly highlights a number of areas in which the Division of Kidney, Urologic, and Hematologic Diseases has reported recent progress in its research program:

- A proposed mechanism explaining progressive renal failure has received experimental support. Initial loss of functional kidney tissue can set up a cycle of deterioration due to excessive demand on, and excess filtration by, the remaining renal (glomerular) tissue.

- Early clinical evaluation of cyclosporine, a new immunosuppressive agent, has shown it to be effective in improving kidney transplant survival and functioning.

- Use of antilymphocyte globulin (ALG) or antithymocyte globulin (ATG) as an immunosuppressive agent has been shown to decrease rejection of kidney transplants and limit the need for other immunosuppressive drugs. In related studies, antibodies to subsets of lymphocytes that mediate rejection have been produced by new, efficient, monoclonal antibody techniques, and preliminary studies have indicated their clinical efficacy in transplantation.

- Sexual dysfunction in uremic men, including those on dialysis, is frequent and may be due in part to zinc deficiency; administration of zinc was found to increase sperm count, testosterone levels, and frequency of intercourse in some patients.

- A well-controlled study has confirmed the value of recipient splenectomy in increasing the functional survival of transplanted cadaver kidneys.

- Painful kidney stone formation and its recurrence, if due to excessive absorption of dietary calcium, can be inhibited and prevented by the newly approved drug sodium cellulose phosphate, which binds calcium in the intestine and prevents its absorption.

- Progress has been made in understanding the tissue changes and hormonal interactions involved in the common disease benign prostatic hypertrophy, which constitutes a serious health problem in aging males.

- Data on frequency of kidney stones in a large health-plan population showed a rate three times as high for men as for women and twice as high for whites as for blacks and Orientals. Rates decreased as educational levels increased. Stones were rare under age 20, and frequency peaked at ages 40 to 59.

- In preliminary experiments, patients with defects in the adult form of their red blood cell hemoglobin (as in sickle cell and Cooley's anemias) were treated with the drug 5-azacytidine, which increased production of the (nondefective) fetal stage form of hemoglobin enough to overcome clinical signs of anemia.

- A new noninvasive method of measuring iron storage in the liver is based on highly sensitive magnetic detection of the iron. Sequential measurements can be made in conditions of iron deficiency or overload (as in hemochromatosis or Cooley's anemia) without the dangers of liver biopsy.

- Erythropoietin, a hormone regulating red blood cell production, can now be detected in tiny amounts by means of a new radioimmunoassay method, using specific antibodies to the hormone to find it. Tracing its interactions should help us to understand such diseases as aplastic anemia and polycythemia.

Kidney Diseases

A Mechanism Explaining Progressive Renal Failure

Prior Findings

Despite general awareness that chronic renal disease typically follows an inexorably progressive course,

there has been little understanding of the mechanism of this progression and of the roles of contributory factors such as dietary protein and hormonal action. There is increasing evidence that loss of functional kidney tissue such as occurs in a wide range of renal diseases (as well as in the process of aging, in some cases) can lead to a progressive deterioration of function of the kidney, which represents a final common pathway leading to renal failure. Observations about the effect of dietary proteins on "renal work" were made several decades ago, and there is a developing concern that modern high-protein diets prevalent in developed countries may have a deleterious effect on renal function and structure in health and in various kidney diseases.

Recent Advances

In an animal remnant kidney model, functional and structural changes have been shown to vary in relation to dietary protein levels. Glomerular disease (focal glomerular sclerosis) may develop and increase in relation to an unfavorable balance between residual kidney function and dietary protein. Proteinuria (abnormal presence of protein in the urine) decreased renal function, and structural changes were noted in diabetic animals. A marked (fourfold) increase in urinary protein excretion within 1 week of ablation of approximately 90 percent of the renal mass was noted in rats. As the whole-kidney glomerular filtration rate in these rats subjected to this degree of ablation fell to about 15 to 20 percent of normal, protein excretion per nephron increased about twentyfold. Macromolecular tracer studies showed that the proteinuria was attributable to defects in both charge-selective and size-selective properties of the glomerular capillary wall. It is postulated that the hyperfiltration, progressive azotemia (increase in nitrogen wastes in the blood), proteinuria, and glomerular sclerosis occurring after renal ablation were due to sustained adaptive increases in glomerular blood vessel pressures and flow rates, possibly secondary to pharmacologic effects of a hormone such as glucagon. Protein excretion and abnormal pathologic changes of the remaining kidney tissue were greater when dietary protein content was higher. Survival was significantly better in the rats on low-protein diet.

The adaptive hyperfunction of glomeruli that results from intrinsic renal disease or from extensive renal ablation ultimately may hasten the progression to renal failure in patients and in animals. Glomerular hyperfiltration that precedes loss of nephron units in the diabetic state may contribute to the initiation and to the progression of diabetic glomerulopathy noted in up to 70 percent of juvenile (type I) diabetic patients. Similar glomerular hyperfunction in rats made diabetic with streptozocin, and in rats with partial-to-5/6 nephrectomies, appear to be caused by initial intrarenal vasodilatation, followed by increases in glomerular capillary pressures and flows.

Research Directions

The current treatment of chronic renal insufficiency, including efforts to control systemic hypertension, urinary tract infection, and secondary hyperparathyroidism, is not directed toward alterations of the hemodynamic mechanism as described above. Current hypotheses suggest that therapies aimed at preventing excessive increases in glomerular pressure and flows (which may be affected by high dietary protein loads) could be introduced as a means to interrupt the downhill progression of clinical renal disease. A major research effort is needed to translate these findings to clinical application. An expansion of studies in the area of hyperfiltration and the contribution of dietary controls in slowing progression of renal failure may provide a key to treatment of the phenomena observed in slow rejection of renal transplants, in the downhill course of some patients with inactive glomerulonephritis, in focal glomerulosclerosis, and in diabetic nephropathy.

Splenectomy in Graft Survival of Kidney Recipients

Prior Findings

Because of the limited supply of donor kidneys from compatible, closely related living donors, the majority of transplant patients with end-stage renal disease receive cadaver kidney grafts. The overall rate of functional cadaver graft survival remains substantially below that for transplants from closely related living donors. In an effort to improve graft survival, scientists have studied the effects of various factors on graft survival, including splenectomy (surgical removal of the spleen).

Retrospective analyses of the value of splenectomy for some transplant groups have shown a beneficial effect in some cases and no difference in others. It has been suggested that splenectomy minimizes the leukopenic (diminished number of white cells) effect of the immunosuppressive regimens necessary for renal graft survival. Since splenectomy is considered a major operation with potential complications, a prospective randomized clinical trial to compare the benefits of splenectomy versus nonsplenectomy in transplant patients was conducted.

Recent Advances

Over a 2-year period, 299 renal allograft patients receiving the same immunosuppressive treatment were

randomized into the two groups, splenectomized and nonsplenectomized recipients, and stratified according to transplant donor type. Graft survival at 2 years was significantly better in the splenectomized recipients of cadaver kidneys than in the nonsplenectomized patients.

Research Directions

Under the standard immunosuppressive regimen, splenectomy should be considered in recipients of kidneys from either cadaver donors or from HLA nonidentical, selected living donors. The relationship between splenectomy and graft survival rate needs to be further characterized in the context of recently improved graft outcomes due to newer approaches to immunosuppression.

Antilymphocyte or Antithymocyte Globulin as an Adjunct Immunosuppressive Agent

Prior Findings

When antibodies are produced against human lymphocytes (white blood cells) or thymocytes (cells of the thymus, an organ concerned with immune responses), the antibodies are found in the blood serum fraction called globulins. When such globulins are injected into a transplant recipient, a marked suppression of cellular immune reactions against the transplanted "foreign" tissue results. Antilymphocyte globulin or antithymocyte globulin can be used to improve early kidney transplant function and control acute rejection.

Both ALG and ATG have been shown to be superior experimentally in prolonging allograft survival compared to the immunosuppressive drugs azathioprine and prednisone, but their clinical effectiveness has been difficult to establish. Some of the reasons for this difficulty are the frequent variability in the potency of batches of ATG or ALG, differences in the dosage schedules followed by different groups of investigators, and insufficient numbers of patients to make a statistically valid evaluation.

Recent Advances

Several clinical studies were recently performed. In the first study, 60 transplant recipients of kidneys from cadavers were given ATG in conjunction with the immunosuppressive drugs azathioprine and prednisone, and 44 patients were given azathioprine and prednisone alone. The ATG-treated group had significantly fewer rejection episodes and a definite decrease in immunosuppressive drug requirements without increase in the incidence of infections. Functional graft survival was 10 to 13 percent higher in the ATG-treated group at all times.

The second study, the Kidney Transplant Histocompatibility Study, enrolled over 1,500 patients for cadaver kidney transplants in a collaborative trial. At all time intervals up to 3 to 36 months after transplantation, graft survival in patients given ALG treatment was 10 to 11 percent better than in those who did not receive ALG.

In the third study, 64 patients received either ALG or the standard antirejection drug regimen. Graft survival was better with ALG (82 percent) than with the standard regimen (61 percent). Second rejection episodes were fewer in the ALG-treated group.

Studies using ALG as an adjunctive immunosuppressive agent in primary cadaveric kidney transplantation show that treatment with ALG results in 10 to 15 percent improvement in functional graft survival for 1 to 2 years, with probably no alteration in patient survival. The incidence, severity, and ease of reversibility of early rejection reactions are improved with adjunctive ALG treatment (and reduced immunosuppressive drug dosage) both in patients with living, related donors and in those receiving cadaveric kidney transplants.

In another study, antibodies to thymocytes (precursors of the T-cell lymphocytes considered responsible for rejection) were prepared using a new technique for producing highly specific (monoclonal) antibodies. The first clinical trials were performed recently using monoclonal antibodies in the treatment of acute rejection of transplanted cadaveric kidneys. In all cases, established rejection episodes were reversed within 2 to 7 days without addition of any therapy other than the monoclonal antibody and despite continued lowering of immunosuppressive drug dosages. During the subsequent 3- to 13-month followup, further rejection episodes occurred in five of the eight patients; six of the original eight renal grafts continued with excellent function.

Research Directions

Continued studies are necessary to delineate more clearly the subsets of lymphocytes that are primarily responsible for graft rejection and not for other vital immunological functions. With such knowledge, more highly selective monoclonal antibodies could be developed for use in preventing or treating transplant rejection.

Improved Graft Survival in Early Use of Cyclosporine

Prior Findings

Cyclosporine, a new immunosuppressive agent that is obtained from two species of fungi, has been shown to greatly increase graft survival and decrease infectious complications in experimental animal models. It is now undergoing clinical evaluation.

Recent Advances

A prospective, randomized, controlled clinical trial compared cyclosporine (combined with a low dose of the steroid drug prednisone) with the conventional immunosuppressive regimen. The conventional immunosuppressive regimen used the drugs azathioprine and prednisone for the duration of graft function and antilymphocyte globulin during the immediate post-transplant period. The study attempted to characterize the role of cyclosporine as a new immunosuppressive agent and its advantages in clinical transplantation.

The initial trial included approximately 120 patients, all of whom showed improved graft function after cyclosporine treatment. There were fewer cases of rejection episodes, fewer infectious complications, and fewer hospitalization days in the cyclosporine-treated patients.

If the current results continue to be promising, cyclosporine could become a standard immunosuppressive agent in renal transplantation and may prolong graft survival and decrease infectious complications and hospital costs.

Research Directions

Further evaluation and refinement of cyclosporine action are required. Its known nephrotoxicity and hepatotoxicity appear to be dose dependent and may be minimized by the use of a cyclosporine radioimmunoassay to guide drug doses. Doses of cyclosporine may need close monitoring for serum levels and possible toxicity in each individual case.

Zinc Deficiency in Uremic Men

Prior Findings

Abnormalities in sexual function are not uncommon among patients with chronic renal failure and among the 70,000 renal failure patients on dialysis. Zinc deficiency has been implicated as a cause of impotence in uremic men. Despite adequate dialysis, zinc deficiency may account for gonadal dysfunction and testicular atrophy. Administration of zinc during dialysis improved serum testosterone levels and impotence in uremic men in at least one study.

Recent Advances

To evaluate more critically the possibility that zinc deficiency is a reversible cause of gonadal dysfunction in uremia, a double-blind study using oral zinc and a placebo was begun, and the effect of zinc or placebo therapy on testicular function and sexual performance was examined. At the end of a 6-month study period, a significant increase was observed in the mean plasma zinc, serum testosterone (male sex hormone), and sperm count of the zinc-treated group. The zinc-treated group also had a significant fall in serum-luteinizing hormone and follicle-stimulating hormone not seen in the placebo group. Patients receiving zinc had an improvement in potency, libido, and frequency of intercourse greater than that of the placebo group. The results of this pilot study support the hypothesis that zinc deficiency and gonadal dysfunction may be causally related to and responsible for impotence in certain uremic men.

Research Directions

A large-scale comprehensive analysis of sexual dysfunction in dialysis patients is needed to ascertain its true incidence and pathogenesis in uremic patients and to elucidate the most effective therapeutic approaches.

Nephrotoxicity of Lithium

Prior Findings

The efficacy and increased use of lithium salts in the treatment of neuropsychiatric disorders have resulted in renewed interest in the nature of their toxic side effects (renal tubular toxicity, chronic tubulointerstitial nephritis, and progressive renal insufficiency).

Recent Advances

The site of the early pathologic lesion due to lithium toxicity and its correlation with a lithium-induced concentrating defect have been reported. There also is a lithium polyuria (increased amount of urine) associated with structural changes of the principal cells of both the outer cortical collecting duct and the medullary (inner) collecting duct. The structural changes are accompanied by alterations of cell volume regulation. Although lithium regularly affects water metabolism by these mechanisms, it is gratifying that cumulative exposure appears to cause progressive renal damage only rarely. Preliminary results of a prospective study involving patients indicate no definitive decrease in glomerular filtration rate in patients on lithium therapy.

Research Directions

Retrospective evaluation and prospective studies are needed to provide objective natural history data on patients treated with lithium chloride on a prolonged basis. Animal studies are needed also to find a suitable therapeutic regimen to reduce the kidney effects of chronic administration of lithium salts.

Ochratoxin A as a Cause of Balkan Nephropathy

Prior Findings

Balkan nephropathy is a peculiar endemic nephropathy characterized by a progressive course

leading to severely atrophied kidneys and death due to uremia. The disease was first recognized in 1942 and occurs in farmers living in the rural areas around the Danubian Iron Gate tributaries. The search for possible causes, such as environmental infections or toxic factors, has been unsuccessful. Ochratoxin A, a mycotoxin and natural contaminant of foodstuffs, particularly in corn and certain cereals, is found in more than 10 countries in Europe and in North America. Ochratoxin A is known to cause nephropathy in a variety of animals, including swine, and recently has been suggested as a possible causative agent of this disease in humans.

The porcine form of ochratoxin A nephropathy is characterized by impaired renal (proximal tubular) function with decreased urinary concentrating ability and increased urinary excretion of glucose, the enzyme leucine aminopeptidase, and proteins. Abnormal tissue changes include degeneration of the proximal tubules, interstitial fibrosis, and hyalinization of glomeruli.

Recent Advances

Several observations provide evidence in support of ochratoxin A as a cause of Balkan nephropathy. Ochratoxin A-associated porcine nephropathy is found in several countries in Europe and has morphologic and functional renal changes comparable to those observed in humans. Further, oral ochratoxin A has caused nephrotoxic changes in all animal species tested thus far. The contaminant has been detected in foods in most countries where surveys have been conducted. An area of Yugoslavia seems to exhibit the highest occurrence of ochratoxin A in foods and in serum samples from inhabitants of this area. The latter finding indicates that ochratoxin A intake does occur. Attempts to identify other etiologic agents known to cause renal disease in areas of endemic nephropathy in the Balkan peninsula have been negative so far.

The activity of renal enzymes such as phosphoenolpyruvate carboxykinase, which is located in the proximal tubule, is blocked in rats fed low doses of ochratoxin A for 2 days. No other enzyme activity measured was found to be affected. Swine were used as an animal model because of the similarity of clinical and pathological findings following exposure to ochratoxin A to those of human cases of Balkan nephropathy. PEPCK activity in renal biopsies of swine fed graded doses of ochratoxin A over a 1-month period is now being measured.

Research Directions

Future study of Balkan endemic nephropathy includes continued evaluation of the possible etiologic role of ochratoxin A. These studies of Balkan nephropathy ultimately may provide additional insight into related nephropathies.

Urologic Diseases

New Drug for Kidney Stone Prevention

Prior Findings

Urolithiasis is the development of stones in people. In industrialized countries, they occur primarily in the kidney and upper urinary tract; in developing countries they are also in the bladder. Passage of a kidney stone is one of the most painful medical disorders and one of the most common disorders of the urinary tract. Research in this area has focused on the mechanisms of formation and dissolution of stones and on means for medical intervention in this process. Five Specialized Centers of Research (SCOR's) in Urolithiasis were initiated in 1977 to increase the knowledge base about the occurrence and treatment of kidney/urinary tract stones.

There are several causes of kidney stone formation. One of the kidney stone-forming disorders is associated with increased absorption of calcium from food. About one-quarter of the U.S. population with kidney stones form calcium stones. Certain of these patients can be treated successfully on a low-calcium diet, along with avoiding excessive salt and vitamin C.

Recent Advances

In clinical studies, the drug sodium cellulose phosphate (SCP) has demonstrated effectiveness in inhibiting painful stone formation in patients whose kidney stones are due to excessive absorption of dietary calcium. Approximately 100,000 patients in the United States fall into this category. Where applicable, SCP is administered orally. Within the gastrointestinal tract, it binds calcium from food, thereby lowering the amount of calcium absorbed into the circulation from the intestines. Because SCP is inert and not absorbed by the gut, it has no significant side effects. One concern raised by investigators in the field is the hazard of causing excessive calcium dissolution from bone. Although SCP does not seem to cause negative calcium balance in patients, it must be used with caution because of this potential problem. When SCP is withdrawn from stone-forming patients, they tend to reform calcium stones; thus continuous maintenance treatment may be necessary.

The Food and Drug Administration recently approved SCP for commercial marketing. This latest action climaxes a significant advance based on research supported for several years by the NIADDK. This represents a major achievement in the prevention of a serious recurring disorder.

Research Directions

Other inhibitors of stone formation are being investigated to correct other types of kidney stone

disorders, especially the recurring type. More studies are needed in this area and are under way in all of the NIADDK's five Specialized Centers of Research in Urolithiasis.

An "Orphan Drug" Blocks Ammonia-Based Stones

Prior Findings

In patients with chronic urinary tract infections, the bacterial organisms present often produce an enzyme (urease) that splits the urea molecule and causes a buildup of ammonia salts in the urine in the form of magnesium ammonium phosphate (struvite). With increased alkalinity, the urine becomes supersaturated with struvite and crystals form, and these become kidney stones. Such stones are thought to represent 15 to 20 percent of all renal stones; these stones typically are massive and cannot be passed or effectively removed surgically. The impact of the disease on patients is severe. About half the patients will lose the affected kidney in 5 years if untreated. With bilateral disease, 25 percent of patients may progress to end-stage renal disease in 5 years, and 40 percent in 10 years. People who are paraplegic are the largest group at risk, because they often have bladder paralysis and are prone to bacterial infection of the urinary tract.

Recent Advances

Institute-supported studies have shown that acetohydroxamic acid (AHA) blocks the action of bacterial urease, preventing the sequence of events leading to formation of struvite stones. On the basis of these studies, the Food and Drug Administration recently has approved the marketing and use of AHA for reducing the urinary alkalinity in bacterial infections of the urinary tract and for blocking the bacterial urease to prevent the development of struvite stones. AHA has been approved as a so-called orphan drug and will soon be readily available.

Research Directions

In view of preliminary evidence that AHA can reduce the further growth of already-formed struvite stones (as well as prevent their initial formation), future additional clinical studies of the drug are indicated.

Urolithiasis Frequency Data in Health Plan Participants

Prior Findings

Urolithiasis is among the most important causes of morbidity of the urinary tract. Reliable rates of occurrence in defined populations are not readily available. In the United States and most other developed countries, stones are most common in the upper urinary tract; whereas in less-developed countries, bladder stones predominate, especially in children. A large percentage of upper urinary tract or kidney stones contain calcium oxalate as their major constituent. Epidemiologic data strongly suggest that environmental factors such as diet, climate, geologic mineral concentrations, and fluid consumption play a strong etiologic role.

Unfortunately, little population-based data have been published on the incidence of urolithiasis in the United States. Most studies of the frequency of urolithiasis have been based on persons hospitalized with stones. More data on the frequency of stones in well-defined populations are needed.

Recent Advances

In an NIADDK-supported project, the frequency of urolithiasis was assessed in a defined population served by the Northern California Kaiser Foundation Health Plan. The study showed that over 90 percent of stones occurred in the upper urinary tract. The majority of stones contained calcium oxalate. Kidney stones were three times more common in men than in women. Although rare before the age of 20, the frequency increased rapidly and peaked in men between the ages of 40 and 59. Rates were approximately twice as high in whites as in blacks or Orientals. The frequency of stones was inversely related to socioeconomic status as measured by level of education. Unavoidably, data such as these are subject to uncertainties, and rates for the study group could be somewhat high.

Research Directions

More data on the frequency and type of kidney stones in defined populations are needed. To aid in the elucidation of the precise etiology and pathogenesis of calcium oxalate stones, the degree of correlation between stone occurrence and standards of living should be established, and the factors responsible for the higher frequency of the disorder in those of lower socioeconomic status (as indicated in the present study) should be identified.

Benign Prostatic Hyperplasia

Prior Findings

Benign prostatic hyperplasia (BPH), excessive growth of the prostate gland with advancing age, results in progressive obstruction of outflow of urine from the bladder. It sets the stage for chronic infection of the urinary tract and is the cause of considerable, costly, and in some cases, risky, corrective surgery. The

disease has been detected as early as age 20. It occurs frequently, with evidence of symptomatic disease in about 45 percent of men at age 45 and near 80 percent in men over 60. Little progress has been made in increasing knowledge of the underlying mechanisms of BPH in man. A dog model of BPH continues to be studied to define tissue-level conditions influencing BPH development; BPH in dog and man seems to be similar.

Recent Advances

Methods have been developed for separating stromal (nonglandular framework) and epithelial tissue of the prostate. Studies suggest that human BPH results from growth potential present in stromal components. In other findings, prostate tissue in aging dogs has been shown to develop increased sensitivity to sex hormones in the presence of decreased testosterone levels and increased dihydrotestosterone levels (both are male sex hormones). Estradiol (a female sex hormone) can increase tissue conversion of testosterone to dihydrotestosterone in dogs and humans. This conversion has been associated with increasing prostate size in canine BPH.

Hormonal and biochemical interactions in the tissues of the prostate have demonstrated correlation with abnormal prostatic growth in certain instances. Scientists believe that understanding of the mechanism of other hormonal and biochemical processes will aid in the development of medical therapy for BPH, which in turn will obviate the need for surgical treatment. Further, it is hoped that this will diminish morbidity associated with surgery, anesthesia, and their complications in the elderly, as well as permit treatment at lower cost to the patient.

Research Directions

Research in this area has as its primary goal the development of a more precise definition of the etiology and underlying mechanisms responsible for BPH. This can be accomplished by increasing the research effort into the physiology and biochemistry of the prostate in both normal and hypertrophied states. Reduction of the conversion of testosterone to dihydrotestosterone may be one possible avenue of treatment, and this possibility must be explored.

Hematologic Diseases

New Approach to Therapy in Hereditary Anemias: Stimulation of Fetal Hemoglobin Synthesis

Prior Findings

In man, primates, and a few other species, there are two well-defined switches in the pattern of hemoglobin synthesis: embryonic to fetal and fetal to adult. Since the defect in sickle cell disease and Cooley's anemia (the production of impaired, abnormal hemoglobin molecules) is manifested in the adult form of hemoglobin but not in the fetal red blood cells, interest in enhancing the synthesis of the fetal form of hemoglobin (HbF) as an effective form of replacement therapy has been high. While many types of experimental techniques to accomplish a reversed switch from adult hemoglobin to HbF have been tried, most of these have not yet been successful.

Recent Advances

Experimental animals previously identified as low producers of HbF responded to 5-azacytidine (an analogue of cytosine, which is a component of DNA) by an increase in their blood HbF. Five-azacytidine was chosen because it cannot be methylated and because the degree of methylation of DNA has been shown to be important in the control of gene activity, especially in gene expression. In the presence of 5-azacytidine, blood HbF in baboons rose from 32 percent to 81 percent. The response occurred from 5 to 7 days after initiation of treatment with 5-azacytidine and remained high 5 to 7 days after the drug was discontinued. In preliminary trials in humans, two sickle cell disease patients and two with Cooley's anemia (thalassemia major) also responded to 5-azacytidine by an increase in their blood HbF content, which reduced the degree of anemia. Work by both NIADDK intramural staff and grantees contributed to these findings.

Research Directions

The development of a drug that can stimulate the synthesis of HbF in amounts sufficient to reverse the anemia of sickle cell disease and Cooley's anemia should be pursued. Such a drug could revolutionize the treatment of patients and potentially alleviate one of the gravest aspects of these diseases. These results need to be confirmed and extended, and the mechanism of action of 5-azacytidine must be further defined. It should also be confirmed that incorporation of 5-azacytidine into DNA leads to HbF formation in the adult (in contrast to young children). Future studies also must include toxicity studies in animals and humans.

Antithymocyte Globulin Treatment in Patients With Aplastic Anemia

Prior Findings

Aplastic anemia is a serious hematologic disorder characterized by bone marrow failure and consequent depression of the levels of all types of blood cells in the circulation, with a prominent deficiency of red

blood cells. Most data suggest that aplastic anemia usually results from absence or defects of hematopoietic stem cells.

There has been considerable recent interest in the participation of the immune system in the regulation of normal hematopoiesis (production of red blood cells). Several studies have indicated that lymphocyte or antibody-mediated suppression of hematopoiesis (red blood cell formation) may be the cause of aplastic anemia. Clinical observations also suggest that abnormal immunity may contribute to the pathogenesis of the disorder. There is no proven effective therapy for patients with aplastic anemia, and the condition is ultimately fatal, except in the case of a successful bone marrow transplantation.

Recent Advances

The efficacy of antithymocyte globulin for the treatment of moderate to severe aplastic anemia was evaluated in a randomized controlled study. Of the 21 patients who received ATG, 11 had sustained improvement in hematopoiesis within 3 months of treatment. Patients who responded to ATG had only a partial response; there was gradual improvement in hematopoiesis, but no patient recovered to the point of completely normal peripheral blood counts.

The severity of bone marrow failure, cause of aplastic anemia, age, and transfusion history had no apparent bearing on treatment outcome. The best results were obtained in patients who received ATG soon after the diagnosis of aplastic anemia had been made.

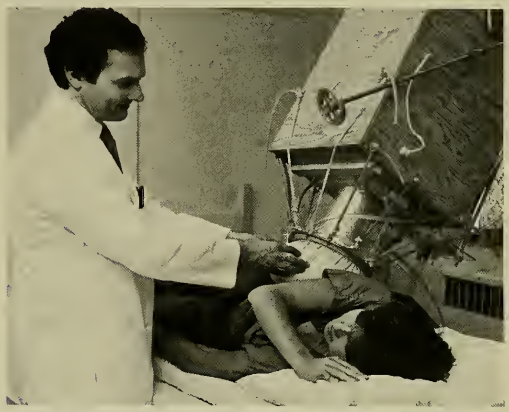
Research Directions

The precise mechanism of response of aplastic anemic patients to antithymocyte globulin needs further study, and the effectiveness and potential toxicity of antithymocyte globulin need to be established.

Valuable New Diagnostic Method: Magnetic Susceptibility Measurement of Human Iron Stores

Prior Findings

Determination of magnetic susceptibility provides a direct measure of storage iron by taking advantage of the paramagnetic property of ferritin and hemosiderin, the major forms of storage iron in human beings. Magnetic measurements of iron stores provide a new quantitative technique for early detection of hereditary hemochromatosis—a disease characterized by excessive, uncontrolled uptake of dietary iron from the gut and tissue-damaging excessive iron stores in vital organs—and for rapid evaluation of treatment regimens for transfusional iron overloads. Both disorders are serious and potentially fatal, and a reliable, noninvasive diagnostic method is needed to follow the course of each disease.



Using a prototype of a newly developed noninvasive iron-storage measurement device, NIADDK researchers can detect potentially fatal tissue iron overloads caused by disease or transfusion.

Recent Advances

Direct noninvasive magnetic measurements of hepatic iron stores were made with a specially designed superconducting quantum-interference-device (SQUID) susceptometer in 110 patients with liver disease, iron deficiency, hereditary hemochromatosis, or transfusional iron overload. Magnetic *in vivo* measurements of liver nonheme iron (iron not being used for hemoglobin) were closely correlated with chemical *in vitro* measurements in liver biopsy specimens. Magnetically determined concentrations of hepatic storage iron were low in iron-deficient patients, normal men, and premenopausal women. Hepatic iron stores were raised in all patients in whom hereditary hemochromatosis was either untreated (including one with a normal iron transport protein, or serum ferritin, level) or partially treated. Magnetically measured liver iron stores were also increased in all patients with transfusional iron overload. The concentrations of storage iron found in the livers of patients with homozygous beta-thalassemia (the homozygous state is the major form of this anemia) who were managed with subcutaneous deferrioxamine (a form of iron-chelation therapy to reduce abnormally high iron tissue stores) were well below those reported in patients who had not received long-term chelation therapy. Because magnetic determinations are noninvasive, safe, and rapid, the technique is particularly useful for sequential observations, and it can supply otherwise unobtainable information on changes in liver (or other organ) iron content due to intestinal absorption, transfusion, phlebotomy, or chelation therapy.

Research Directions

This powerful new technique should be used in studying the mechanisms underlying iron diseases and iron deficiency diseases. The technique should also provide a powerful tool for testing and evaluating therapeutic methods for iron storage diseases.

Reduction in Messenger RNA Production in Red Blood Cells of Cooley's Anemia Patients

Prior Findings

Thalassemia major, or Cooley's anemia, is a severe, inherited blood disorder seen largely in persons of Mediterranean ancestry. In these individuals, the red blood cells that normally carry the oxygen-transporting pigment hemoglobin are destroyed by the body shortly after development of the cell because the hemoglobin production within each cell is abnormal. The result is severe anemia, a lifelong dependence on blood transfusion, and death by the third decade of life. Abnormalities in the genes result in production of anomalous hemoglobin (the globin portion of the molecule is defective), which causes the disease. Until recently, the precise mechanism and structural basis for the abnormality were poorly understood. The lack of appropriate technology was responsible for this gap in knowledge.

Recent Advances

Three important technical advances have made it possible to obtain genetic information. The first advance, improved cell-free translation systems, takes advantage of RNA molecules. RNA molecules are copied from DNA, the genetic material in the chromosomes, by the process of transcription. The genetic code is translated from the RNA into the specific protein molecules the code represents. Recent advances have made it possible to conduct the translation process in a laboratory from synthetic or cellular components in the absence of intact cells.

The second technique involves molecular hybridization. With the help of reverse transcriptase, an enzyme obtained from viruses, one can take RNA and reverse the process of transcription thereby obtaining DNA of known genetic composition. Using molecular hybridization techniques, the copied DNA is inserted into a bacterial chromosome and copied many times (cloning). The large quantities of DNA thus obtained make it possible to study the structure and activity of this synthesized DNA.

The third advance, new rapid nucleotide sequencing techniques, allows rapid determination of the base sequences (and thus the chemical composition) of very small quantities of RNA and DNA.

Results indicate that Cooley's anemia is caused by a quantitative reduction in specific messenger RNA's produced by the red blood cells. In beta-thalassemia, total absence of beta globin messenger RNA is observed in some cases, while in other cases, a reduced amount of beta messenger RNA can be detected. In one case, the defect has been found to be a "nonsense" mutation of no function. A single nucleotide change causes premature termination of the synthesis of beta globin chains in the hemoglobin molecule. It is not known whether this latter defect is a general phenomenon. Other forms of mutations resulting in thalassemia are being investigated.

Research Directions

Future research will focus on improvement of methods to study globin gene transcription and globin mRNA metabolism in humans, particularly in human bone marrow cells. Clarification of the detailed structure of the messenger RNA's and their respective globin products will make it possible to understand the molecular basis and pathophysiology of the various forms of these clinically important diseases. Appropriate therapies may then be devised.

Inhibition of Iron Absorption by Dietary Calcium in Iron Deficiency Anemia of Infants

Prior Findings

In infancy and childhood, iron deficiency is common because of high iron requirements for growth and the heavy consumption of milk, a food with high calcium but low iron content. Experiments in rodents suggested that excessive dietary calcium levels are associated with reduced inorganic iron absorption; however, none of these experiments used methods that measured iron absorption directly, depending instead upon body retention of the absorbed iron. Human studies were equally inconclusive.

Recent Advances

Investigators recently have shown that the concomitant presence of calcium in the intestine decreases the entry of iron into intestinal epithelial cells. Electron-microscopic observations and quantitative studies in rats showed that more iron is absorbed using human milk as a calcium source than using either milk from cows or human milk supplemented with calcium. Convincing evidence was obtained that, at physiologic concentrations, dietary calcium inhibits iron absorption by competing for shared pathways in the small intestinal mucosa (inner lining). Animals fed a high-calcium diet with amounts of iron normally sufficient for good

health developed iron depletion, an outcome similar to that found when cow's milk (which is rich in calcium) was used instead of human milk.

Research Directions

Studies will be designed to clarify rates and conditions of iron absorption in the presence of calcium. Also needed are elucidation of the effects of calcium on iron binding at specific subcellular sites and characterization of iron receptors in intestinal cells.

Radioimmunoassay for Purified Erythropoietin

Prior Findings

Erythropoietin is a glycoprotein hormone composed of 10 to 15 percent sialic acid and 50 to 60 percent carbohydrate and is responsible for stimulating and controlling the production of red blood cells by the bone marrow. It is produced by the kidney in response to certain stimuli—primarily alterations in oxygen delivery to the kidney. Little is known about the structure and physiological-hormonal action of erythropoietin. There is considerable controversy whether the active form of erythropoietin is generated intact or undergoes a series of modifications in the blood after release from the kidney. In the past, because erythropoietin was not available in large quantities, it was difficult to study it at the molecular level. Patients with chronic renal failure develop anemia due to the loss of functional kidney tissue and the resulting strong decline in erythropoietin synthesis. For effective prevention or treatment of the disabling anemia of renal failure, it is necessary to generate erythropoietin on a large enough scale and to administer it to patients as replacement for their own missing erythropoietin. Alleviation of the anemia substantially improves the quality of life (and ability to do physical work) of renal patients.

Recent Advances

Human erythropoietin has been purified from human urine by "hydrophobic" laboratory chromatography, which makes use of lectins (plant components that bind carbohydrates). With the purification of erythropoietin, it is possible to develop a specific radioimmunoassay for erythropoietin sensitive enough to detect the glycoprotein in extremely small amounts. As a result of improved technology, the purification of erythropoietin has been simplified greatly, although the yields still need improvement.

Research Directions

With the purification of erythropoietin and the development of a sensitive radioimmunoassay, it now will be possible to discover the sites and characteristics of cell membrane surface receptors for erythropoietin, the conditions under which cells are responsive to erythropoietin, and its action on intracellular events in both normal hemopoiesis and hemopoietic diseases, such as aplastic anemia and polycythemia.

Also of considerable interest is the further elucidation of the mechanism of the anemia of renal insufficiency, since it now will be possible to examine precisely the proposed role of erythropoietin (and its lack) in red blood cell synthesis in these anemic patients.

Program Accomplishments

The Division of Kidney, Urologic, and Hematologic Diseases conducts a variety of activities to support and stimulate research within its subject areas. In addition to funding specific studies, the staff assists in identifying new research opportunities, assessing research progress, and publicizing findings and new methods of treatment. The Division holds conferences of experts to advise the Institute on progress and research needs, to assess agreement among scientists about the best current treatments, and to determine the best way to educate the clinical and patient community about new developments. Based on these conferences, the Division publishes program announcements and requests for proposals in the areas where high-priority research needs have been identified. The Division also publishes a variety of scientific and educational materials and disseminates information concerning new research directions for investigators in the field.

Conferences

Conferences on research and clinical developments and advances in biomedicine facilitate the immediate exchange of information and cross-fertilization among those working in the field and are an important part of the NIADDK program. Personal discussion with peers is the most rapid and effective way of both sharing new knowledge and stimulating the pursuit of new directions and is the fastest and most effective cross-fertilization process in biomedical research.

In the past year, the Division of Kidney, Urologic, and Hematologic Diseases has supported or shared responsibility for supporting nine scientific conferences, including:

- International Conference on Aplastic Anemia
- Joint Conference on Normal and Neoplastic Hematopoiesis (participating with the National Cancer Institute)
- Joint Conference on Recent Advances in Bone Marrow Transplantation (participating with the National Institute of Allergy and Infectious Diseases)

- Conference on Hydrogen Ion Transport in Epithelia
- Workshop on Techniques in Developmental Renal Research
- International Conference of the Society of Experimental Hematology (participating with the National Heart, Lung, and Blood Institute)
- Third International Workshop on Ammoniogenesis
- Conference on Regulation and Development of Membrane Transport
- Gordon Research Conference on the Red Cell

In addition, awards were made permitting attendance of U.S. participants in the 29th International Physiological Congress.

Announcements Requesting Applications or Proposals

When the Division identifies an area of high-priority need but receives few applications in that area, it develops an announcement to alert investigators in the field to new funding opportunities. In the past year, the Division has published several new announcements. A Request for Applications (RFA) for a Cooperative Agreement Program for a Multicenter Collaborative Clinical Study of Dietary Modification on the Course of Progressive Renal Diseases was issued in August of 1983. This RFA evolved from the program interest entitled "The Natural History and Mechanisms of Chronic Renal Disease." The background of this program emphasis is discussed in the section "Program Plans."

A program announcement entitled "The Immune Basis of Renal Disease" has identified research areas intended to provide greater insights into the immunopathogenetic mechanisms that may cause renal injury. Some of the research areas include:

- Studies to define better the role of lymphoid cells, which may directly produce renal injury or may cause disordered humoral immune responses.
- Development of new markers and new ways of assessing functional activity of cells within infiltrates developed during the immune response.
- Studies of purported nonimmunologic mechanisms that may influence immunologically initiated renal diseases.
- Basic laboratory or clinical studies that have relevance to immunologic basis of renal disease.
- Investigation of host factors that predispose to the development of antibody-mediated injury.
- Studies to define the role of cell-mediated immunity in glomerulonephritis.
- Development of animal models in which cell-mediated injury is demonstrable.

Program efforts have also concentrated on stimulating more research on benign prostatic hyperplasia. A program announcement was issued reemphasizing the NIADDK's continuing interest in studies on the onset and progression of BPH, the potential medical therapeutic modalities for its treatment, and the uropathy associated with it. Background information on the BPH announcement is presented under "Program Plans."

Continuous Ambulatory Peritoneal Dialysis

Support for the National Patient's Registry is continuing, with the fiscal year 1983 recompeting of contracts for operation of the clinical centers and the data coordinating centers.

Evaluation of the Hematology Program and of Hematology Research Needs

A major evaluation of research in hematology in relationship to the NIADDK program has now been completed. The project was initiated to analyze the current state of research in hematology, identify gap areas and the technological advances needed to close them, assess the need for a detailed study of hematology research manpower, and evaluate the extramural hematology program of the NIADDK in relation to the identified needs. The purpose of the evaluation was to (1) provide a rational basis for planning to meet the needs for fundamental and clinical research on hematologic diseases, (2) analyze and evaluate overlap with other NIH programs and the means for resolving any overlaps, (3) identify areas of research not receiving sufficient emphasis, (4) identify new or static areas of research that would benefit from stimulation, and (5) explore the need for a detailed study to assess manpower needs for research. The study was supported by a contract under which a steering committee of consultants oversaw the activities of about nine work groups addressing areas of hematology research within the NIADDK's mission. Close coordination with the blood programs of other NIH BID's was maintained.

The result of the evaluation was the production of information useful in formulating a plan for allocation of resources according to realistic research priorities. The information presented in a working paper will be updated periodically. This working paper will be useful in determining the directions of research support by the NIADDK, in assisting evaluation of grant proposals within the Institute, in assisting scientists at research

institutions in developing their own priorities in the choice of research direction, in providing the various legislative bodies and executive agencies responsible for evaluating priorities in this field with an assessment of needs and opportunities in hematology by experts working in the field, and in providing the public with information concerning the prevention and cure of hematologic disease. The scope of research to be considered will range from that leading to an understanding of the basic mechanisms of normal function and the pathogenesis of disease through development of treatment modalities and the clinical application and evaluation of treatment.

Program Plans

A Funding Program for Work on Polycystic Diseases

The polycystic diseases of the kidney include two principal entities: infantile polycystic disease of autosomal recessive inheritance and adult polycystic disease of autosomal dominant inheritance. The latter, a significant disease process, affects 200,000 to 400,000 Americans and is responsible for 9 to 11 percent of patients on ESRD programs. This genetic disorder usually does not express itself until the third to fifth decade, when the opportunity for its transmission usually has occurred. In fiscal year 1982, it was estimated that the ESRD program supported by Medicare approached $1.8 billion and, of these costs, approximately $180 million was for polycystic disease patients. The loss of work and the human costs escalate this figure even further.

Very little is known about the natural history of the disease, and little is known about its pathogenesis. There is some experimental evidence that the basement membrane of the affected tubules is abnormally compliant. It has been shown experimentally to be a slowly progressive condition that affects renal tubules and is characterized by progressive focal increases in their diameter until they reach enormous proportions and eventually choke off the normal surrounding nephrons. Two theories to explain the possible mechanisms for the renal cyst development have been proposed: (1) a primary defect in the basement membrane that permits cyst formation and (2) cyst formation due to the obstruction of urine flow downstream from the cysts; obstruction is said to be due to polyps, but these occupy only a fraction of the luminal area and have been found only sporadically in afflicted nephrons.

This initiative will attempt to stimulate research interest in the polycystic diseases by providing the necessary funding, especially for investigators concerned with the basement membrane of the renal tubules and its pathology.

Pathways to the Prevention of Renal Failure

It is estimated that 60,000 Americans were maintained by dialysis in 1981, while over 4,000 new patients with irreversible kidney disease entered dialysis treatment programs. During the same period, 4,800 patients received kidney transplants. The cost of these treatment modalities, underwritten by the Federal Government, approached $1.5 billion, primarily through Medicare. It is therefore important to maintain a major research thrust directed at the ultimate goal of arresting or preventing the diseases that lead to chronic renal failure. For example, it is known that after experimental uremia produced by surgical ablation or infarction of renal mass, the residual renal tissue undergoes progressive hypertrophy/hyperplasia and there is increased filtration by remnant glomeruli. For 50 years, it has been recognized that removal of three-fourths or more of the renal mass in the rat (by surgical resection, infarction, or a combination of these maneuvers) causes a progressive azotemia, proteinuria, and arterial hypertension. Striking structural alterations occur in these residual glomeruli during the process of adaptation, and eventually glomerulosclerosis occurs. Hyperfiltration into surviving nephron units was considered a beneficial adaptive response because the decrement in total glomerular filtration rate (GFR) caused by nephrectomy was alleviated partially. There is increasing evidence to suggest that these increased GFR's may be deleterious ultimately and that glomerulosclerosis is caused by glomerular hyperfiltration in the rat. Since many aspects of therapy in renal disease and in diabetes mellitus have been used that consider the initial increase in GFR beneficial, a new view may need to be adopted if these observed correlations of adaptive increases in GFR followed by glomerular sclerosis in animals are proved to occur in humans.

Recent studies have reemphasized the potential role that a number of factors (e.g., protein and phosphate intake, hormones, hypertension, and thyroxine) may play in causing renal disease to progress. The relative importance of these factors and the mechanisms by which they may accelerate progression of renal disease have not been examined fully. Much basic and applied research (laboratory and clinical) needs to be done in this area. The recent comprehensive hypothesis of Brenner, which focuses on the progressive deterioration in kidney function seen in renal disease and in normal aging, needs to be examined. Were we to find the means to slow or prevent the progression of chronic renal disorders, the number of patients requiring chronic hemodialysis or transplantation could be diminished, human suffering would be alleviated, and the overall costs of treatment of patients with ESRD would be diminished.

Cooperative Clinical Study of Early Renal Failure

Current basic knowledge is still remarkably limited as to the natural history and underlying mechanisms of renal diseases progressing to chronic renal failure. Much is to be learned if the social, economic, and human distress brought about by renal failure is to be alleviated.

Through a multicenter cooperative clinical study that emphasizes the role of dietary protein restriction in prevention of further progression of early renal disease, this initiative will attempt to:

- Document rate of progression and course of the disease process in patients with stable, slowly progressing, and more rapidly progressing decline in renal function.
- Define the characteristics of patient subgroups during a pilot phase.
- Investigate factors responsible for presentation, transition, and progression toward chronicity after the initial assault.
- Delineate the role of metabolic-nutritional parameters influencing the course of renal diseases.
- Evaluate outcomes over time of present therapeutic measures and closely monitored dietary patterns in well-characterized patients.

This initiative is based on studies over the past several decades that have indicated that major adaptations in residual nephrons occur following loss of renal parenchyma. Observations in animal models indicate that mechanisms that normally emerge to compensate for glomerular injury may themselves become maladaptive and propagate additional nephron loss. In related clinical observations, dietary restriction has been suggested to exert a favorable effect on the rate of progression of several chronic human renal diseases. This conclusion is regarded as tentative and unproven because of the lack of rigorous controls in most of the reported studies and the absence of statistical analyses of the influence of covariates other than nutritional intervention on outcome. Two statutory requirements (P.L. 95-292 and P.L. 96-499) mandate research pertaining to the effect of dietary modification in chronic renal disease.

A New Program Emphasis on Benign Prostatic Hypertrophy

The high incidence and the prevalence of BPH in older men, with its potential for producing obstructive uropathy, account for BPH being the leading cause of kidney and urinary tract disorders. Modern techniques for accurate measurement of prostate size and advances in radioimmunoassay of hormones utilizing specific titers of antibodies make this a most opportune time for accelerated research effort in this area. Progress in the past 2 to 3 years has made it possible to study the physiological and biochemical nature of the underlying causes of this disease. It is hoped that such studies will facilitate medical management of BPH. Effective medical management will obviate the need for surgery and its associated hazards in the elderly.

A program announcement will invite investigators to undertake the following studies:

- Develop alternatives to surgery for treating BPH.
- Assess the interrelationships of anterior pituitary and sex hormone plasma (serum) levels with precise quantification(s) of prostate size in the onset and progression of BPH.
- Explore more intensively the physiology of receptor systems in both normal and diseased prostate tissues.
- More fully characterize the contribution of the testes to the onset and progression of BPH by using gonadotropin-releasing-hormone agonists and antagonists; this approach would obviate the necessity of castration, which may potentially affect liver uptake and clearance of serum (plasma) hormones.

Conference on Shock Wave Destruction of Renal Stones

Medical treatment and the surgical removal of stones are the most frequent approaches to handling patients suffering from urinary tract stones. Urinary tract stones are among the most common problems treated by urologists, and it is estimated by some that the frequency of occurrence is about 1.2/1,000 population. This Division has continued to emphasize urolithiasis research to increase understanding and knowledge of the mechanisms underlying formation and dissolution of kidney stones.

A new technique for noninvasive removal of kidney stones uses high-energy shock waves to disintegrate kidney stones. This technique, developed in Europe, has been evaluated in dogs and in humans. It has been effective in the majority of cases and has not produced deleterious side effects. The apparatus is on the market at a cost of about $1.5 million. Two or three U.S. clinics are assessing high-energy shock wave generation. Several clinics in the United States are developing other techniques to destroy stones noninvasively.

This conference will convene experts from several disciplines with these objectives in view:

- To develop alternatives to surgery for destroying renal stones.

- To explore energy sources for generating shock waves and less expensive alternatives to X-ray for locating stones *in vivo*.

Red Blood Cell Enzymes: New Techniques Needed

The nature and importance of critical enzyme-mediated reactions in circulating human red blood cells have been elucidated. The 1956 demonstration of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency-induced hemolysis in certain individuals was a signal development. Pyruvate kinase (PK) deficiency was found later in other cses of hemolytic anemia. These two deficiency states make up the largest number of known red blood cell enzyme disorders, with G-6-PD deficiency affecting 100 million people worldwide, while documented cases of PK deficiency number in the hundreds. Another 35 distinct enzymopathies (enzyme deficiencies) have been identified. Some serve as useful markers for the detection and study of multisystem deficiencies that are functionally significant in other organs, including galactosemia, erythropoietic porphyria, megaloblastic anemia, Lesch-Nyhan syndrome, and hereditary methemoglobinemia.

Studies of erythrocyte enzyme defects have made significant contributions toward understanding normal cell metabolism and function. Since these genetically induced molecular lesions result in alterations at single, highly specific points within complex biochemical pathways, studies of the effects of these alterations add to knowledge about the metabolic mechanisms that operate within normal cells.

The most comprehensive studies have been done with G-6-PD. This enzyme's structural and genetic detail is known nearly as well as hemoglobin's. Molecular characterization studies of other normal or defective red blood cell enzymes have been hampered by the low quantity of enzyme proteins in circulating red blood cells, the large subunit size of many of them, and the instability of many of the defective forms. Recent work with partially purified preparations, most notably PK, has demonstrated the existence of previously unknown phenomena of postsynthetic processing and modification, and others. Postsynthetic processing has been found to be a general mechanism in the formation of functioning enzymes and consists of deletions or additions to the fully formed protein or rearrangements of its component parts. Since defects in metabolism are often at highly specific enzymatic points within complex biochemical pathways, studies of red cell enzymes have contributed significantly toward understanding normal cell metabolism and function. Advances include:

(1) The discovery of a previously unknown enzyme, pyrimidine nucleotidase. Discovered as a result of studies in a form of hereditary anemia, pyrimidine nucleotidase is now known to be part of a mechanism of all normal cells to dispose of RNA degradation products during cellular maturation.

(2) The finding of a crucial cellular mechanism of nucleotide salvage, involving plasma adenosine use by adenosine kinase, from studies of red blood cell adenosine deaminase.

(3) Illumination of the complexity of multiple feedback controls operating in anerobic glucose metabolism (glycolysis) from study of glycolytic enzymopathies.

Future research depends on the development of refined microtechniques for enzyme protein isolation and purification. Such techniques could be applicable to common enzymopathies and would lead eventually to amino-acid sequencing, three-dimensional structure analysis, and determination of interrelations with other functional and structural components of red blood cells. In addition to contribution to the basic knowledge of cellular biology and pathophysiology, there would be practical benefits to blood banking, where shelf life and posttransfusion viability of stored cells may be improved considerably by optimal manipulation of their metabolic potentials.

The erythrocyte is a simple model for studying cell aging and can serve as a paradigm for similar investigations in more complex systems. Studies on acquired enzyme abnormalities can increase understanding of regulatory mechanisms of enzyme synthesis, mechanisms of stem cell differentiation and development, and ultimately, mechanisms of carcinogenesis.

Under the intended plan, the Hematology Program will schedule an initial research workshop. Experts in the fields of red blood cell enzymes, biochemical microassay techniques, molecular biology, and allied fields will be convened to discuss the state of science of enzyme isolation and purification, especially as applicable to red blood cell enzymes. This workshop, to be held in fiscal year 1984, would result in specific suggestions for areas of development for microassay techniques. The suggestions would be incorporated into a request for applications anticipated to be issued in fiscal year 1985.

The overall objective is to improve the basis for developing treatment and cures of anemias and other diseases by understanding the biochemical function and biomedical roles of cellular enzymes present in very small amounts in cells, particularly red blood cells. The focus of efforts to achieve this objective will be through development of refined microtechniques for enzyme protein isolation and purification applicable to normal or defective erythrocyte enzymes important in cellular metabolism and function and through development of single-cell quantitative enzyme assays.

The Separation of Blood Cell Precursors: New Methods Needed

Normal blood cell formation (hemopoiesis) is a series of differentiation events beginning at the undifferentiated (pluripotent) bone marrow cell and culminating in the release of functional blood cells. Dramatic improvements in the use of *in vitro* assays for morphologically unrecognizable blood cell progenitors have facilitated the quantitation of the progenitors and the definition of their physical properties.

Elucidation of the mechanisms by which pluripotent cells are committed to one or another blood cell pathway is the central current research issue. Pluripotent cells in culture form colonies of cells, exhibiting several stages of differentiation. Colonies containing up to five types of differentiated blood cell elements (erythrocytes, granulocytes, monocytes, eosinophils, and megakaryocytes) have been described.

Many assay systems designed to emphasize growth of particular subpopulations have been developed. Soluble growth factors and a variety of cell interactions have been identified, many of which are completely artificial and limited to the tissue culture system. A few investigators have designed systems from which homogeneous colonies representing pluripotent stem cells or certain other types of stem cells can be plucked out with relatively high purity. Such purification has been difficult to achieve. Large-scale purification of target cell populations is necessary to understand cell behavior at the molecular level in a setting where both self-replication and multiple paths of differentiation are possible. Once pure subpopulations are obtained and made generally available, the study of factors and interactions will be simplified.

More rapid clarification of mechanisms of stem cell development, which is critical to development of rational therapy for clinically important problems, such as aplastic anemia, bone marrow transplantation, and the leukemias, would be a valuable addition to the clinical armamentarium.

By encouraging applications for research support, this initiative should contribute to the overall objective to optimize the study of early events in bone marrow stem cell differentiation, in order to increase information needed to understand and prevent or cure stem cell diseases. The immediate purpose is to facilitate efforts of investigators to develop techniques for obtaining homogeneous populations of cells from hemopoietic culture systems for subsequent study, to apply new technologies to identify cell surface markers and other functional differences of cells, and to develop libraries of antibodies for hemopoietic cells.

VI. Annual Reports on Evaluation of Multipurpose Arthritis Centers and Diabetes Research and Training Centers

Preface

The Public Health Service Act, which mandates a program of Multipurpose Arthritis Centers and Diabetes Research and Training Centers at NIADDK, also directs that the activities of these centers be evaluated each year and be reported to Congress. The center evaluation reports for fiscal year 1983 are presented in this chapter.

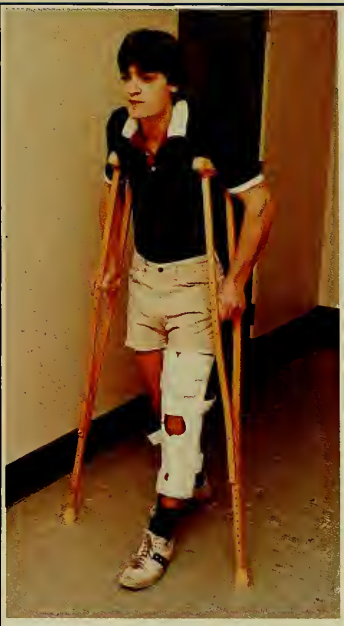
Exhibit 6 (chapter I) lists and identifies the 20 Multipurpose Arthritis Centers and the 7 Diabetes Research and Training Centers supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases in fiscal year 1983.

Seventh Annual Report on Evaluation of Multipurpose Arthritis Centers

Introduction

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases initiated the Multipurpose Arthritis Centers program in fiscal year 1977 in response to the National Arthritis Act of 1974 (P.L. 93-640), which first authorized a national program of comprehensive arthritis centers. The current NIADDK Multipurpose Arthritis Centers are authorized under Section 439 of the Public Health Service Act, and are listed in exhibit 6 (chapter I). Funding levels are shown in exhibit 12. They are designed: (1) to demonstrate and stimulate the prompt and effective application of available knowledge to the treatment of patients with arthritis and related musculoskeletal diseases; and (2) to develop new knowledge essential for the control of these disorders.

To this end, the centers are expected to develop and effect programs in basic and/or clinical research, professional, patient, and public education, and community-related activities and health-services research. A major goal of the NIADDK is to encourage each center to achieve an optimal balance among the three essential operational components, while developing special competence in one or more fields. This report will concentrate primarily on highlighting some examples of the studies conducted during the past year that are reflective of the diversity of the centers program. These highlights, while indicative of activities of all centers, are by no means to be considered comprehensive for 1983.



NIADDK continues to support development of better joint replacement materials and devices. Advances in reconstructive surgery for arthritis are especially important for younger patients in whom prosthetic joints are apt to fail with strenuous use over long periods.

Facing page
Diabetes Research and Training Centers promote training of postdoctoral fellows for research in diabetes and its management.

Center Research Projects

Inherent in the concept of a MAC is a strong research component. Center grant support is intended to complement traditional research grant support in a given institution, to establish related special projects, and to stimulate the development of new research projects. Consequently, each potential MAC is expected to be receiving research grant support for basic and/or clinical biomedical research related to rheumatic diseases as a prerequisite for a center grant award. Each center, therefore, possesses a substantial research base permitting it to examine the cause of rheumatic diseases and, often, to study the means of improving their diagnosis and treatment.

EXHIBIT 12. Funding levels of Multipurpose Arthritis Centers in FY 1983 (dollars in thousands)

Boston University School of Medicine, Boston, Mass.	$855
Brigham and Women's Hospital, Boston, Mass.	484
Case Western Reserve University, Cleveland, Ohio	665
Dartmouth Medical School, Department of Medicine, Hanover, N.H.	388*(1982)
Indiana University School of Medicine, Indianapolis, Ind.	327
Johns Hopkins School of Medicine, Baltimore, Md.	278*(1982)
Medical College of Wisconsin, Milwaukee, Wis.	197*(1981)
Stanford University School of Medicine, Stanford, Calif.	373
State University of New York, Downstate Medical Center, Brooklyn, N.Y.	323
University of Alabama School of Medicine, Birmingham, Ala.	420
University of Arizona College of Medicine, Tucson, Ariz.	308
University of California School of Medicine, San Francisco, Calif.	394
University of Cincinnati Medical Center, Cincinnati, Ohio	166*(1981)
University of Colorado Health Sciences Center, Denver, Colo.	264*(1982)
University of Connecticut School of Medicine, Farmington, Conn.	537
University of Michigan Medical School, Ann Arbor, Mich.	511
University of Missouri Medical Center, Columbia, Mo.	193
University of North Carolina Medical Center, Chapel Hill, N.C.	325
Vanderbilt University Medical Center, Nashville, Tenn.	195*(1982)
Washington University School of Medicine, St. Louis, Mo.	360

** Previous years' levels indicated where a renewal application is currently being reviewed.*

Biomedical research projects supported by center grant funds are almost exclusively development and feasibility studies. These studies are designed to encourage investigators to explore interdisciplinary and highly innovative scientific approaches that may later form the basis of applications for traditional research grant awards from the National Institutes of Health or other agencies.

Investigators at the Case Western Reserve University arthritis center in Cleveland are studying a substance known as C-reactive protein (CRP), a molecule synthesized by the liver in response to tissue injury, with a view to understanding its role and biological significance in acute inflammation. Their first efforts are focused on determining the mechanism of CRP induction and how its biosynthesis is regulated. To do this, molecular genetic techniques are being used to examine how messenger RNA is formed both in normal rabbit livers and from rabbit livers 24 hours after they have been subjected to to an inflammatory stimulus. Initial results have shown, unexpectedly, that even after such a stimulus, no increase in mRNA formation occurs. This is a surprising finding because theory would have predicted more mRNA to be present as a consequence of inflammation. Future experiments will analyze CRP mRNA immunochemically to attempt to explain this anomalous result.

Another study involving immunology is being conducted by the University of Missouri's arthritis center in Columbia, where investigators are using monoclonal antibodies to study autoantibodies in rheumatic disease. The presence of autoantibodies recognizing a number of specific nuclear antigens (the RNP and Sm antigens) is a characteristic feature of autoimmune disorders associated with rheumatic diseases in humans and mice. Mechanisms providing the stimulus and maintenance of these antibody responses, the types of antigens recognized by the antibodies, and the nature of the immune response, still remain to be defined. To examine these questions, the center has been producing hybridomas (artificially produced immune cells that each manufacture a single type of antibody to a specific antigen) that produce antibodies to the nuclear antigens being studied. It has been discovered, so far, that most of the hybridoma-produced antibodies are of the IgM class and that they detect small protein antigens associated with the cell nucleus. Further work on this system will involve characterization of these antigens as well as of those antigens associated with other, related rheumatic disorders.

As one of its developmental and feasibility studies, the arthritis center at the University of Alabama in Birmingham is investigating the role of proteoglycans (a constituent of cartilage) in degenerative joint disease (osteoarthritis). The major aims of the research are to establish an animal model or osteoarthritis, to study the biochemical changes occurring in cartilage proteoglycan, and to determine whether similar biochemical changes occur in the proteoglycans isolated form normal and from osteoarthritic human knee cartilage. Experiments on the animal model (the STR/IN strain mouse) have indicated that the proteoglycans synthesized as osteoarthritis develops are normal in molecular size and structure. Thus, the cartilage destruction that occurs in osteoarthritis must result from other metabolic factors, such as increased proteoglycan turnover,

increased extracellular degradation, or decreased biosynthesis. The fact that the animal model is the mouse has necessitated the development of semimicro isolated methods for the isolation of undegraded cartilage components. These methods will be particularly useful in analyzing normal and osteoarthritic human articular cartilage, which usually are available only in small quantities.

Two of the centers are currently studying the effects of total lymphoid irradiation in the treatment of two rheumatic diseases: rheumatoid arthritis and lupus nephritis. The center at Brigham and Women's Hospital in Boston has managed to suppress disease activity in 6 of 10 patients with rheumatoid arthritis by using total lymphoid irradiation. The treatment resulted in a smaller number of swollen joints, faster walking time, and decreased morning stiffness. Also, the number of circulating immune cells decreased. These data provide evidence that total lymphoid irradiation can induce prolonged, though temporary, alterations in the manifestations of rheumatoid arthritis and suggest that changes in immunoregulation account for this phenomenon. Similarly, investigators at Stanford's MAC have used lymphoid irradiation to treat patients with severe lupus glomerulonephritis. In all cases, the patients' disease could not be controlled by conventional therapy. After irradiation treatment, levels of anti-DNA antibodies (a diagnostic indicator of disease) decreased, serum complement levels returned to normal, and kidney function improved significantly. Studies such as these indicate that total lymphoid irradiation can be useful in treating previously intractable forms of several of the rheumatic diseases.

Another potentially useful treatment for rheumatic diseases emerging from the centers involves the use of monoclonal antibodies to treat systemic lupus erythematosus. In a mouse-model system, investigators at Washington University's arthritis center in St. Louis have succeeded in delaying the onset of lupus nephritis and the appearance of anti-DNA antibodies by injecting monoclonal antibodies specific for double-stranded DNA. Experiments are in progress to determine if any residual anti-DNA remains in the serum after treatment and how administration of these antibodies affects the immune system in general.

A continuing study at the Johns Hopkins University center in Baltimore is concerned with the genetics of rheumatic disease in a highly inbred population: the Old Order Amish. Center personnel have shown that there is a 24-percent prevalence of sacroiliitis in two Amish kindreds. In this population, the presence of sacroiliitis correlated neither with the medical history and physical examination nor with any known histocompatibility (HLA) specificities. This finding indicates that genetic factors other than HLA may be contributing to the high prevalence of sacroillitis in this group of people. In addition, environmental factors may be involved and warrant further study.

A new model of osteoarthritis has been developed at the University of Michigan's arthritis center in Ann Arbor using an extra-articular surgical technique in guinea pigs. Animals that have had their gluteal muscles or infrapatellar ligaments resected were found to have developed some of the typical changes found in osteoarthritis, including joint-space narrowing in the hip and knee joints, pitting of the femoral head, and cartilage thinning. It was significant, however, that no evidence of inflammation was found in any of the joint tissues. The procedures that have been developed at this center offer an opportunity to study early events in osteoarthritis uninfluenced by postoperative inflammation or intra-articular joint trauma.

Center Education Projects

Another integral aspect of the MAC program is the use of educational activities designed to facilitate and increase the education of all types of health professionals. As an example, over the past 5 years, the MAC at the University of Arizona in Tucson has been using patient-instructors (PI's) to teach medical students, residents, practicing physicians, and allied health professionals about arthritis. Patient-instructors are individuals who have been taught to use their own musculoskeletal abnormalities as teaching material. Several reliability studies have been conducted to assure agreement and equality of scoring among the PI's, and a manual, *Physical Examination of the Musculoskeletal System*, was written to aid students in perfecting their techniques of examination and recognition of abnormalities. This manual is designed to be used in conjunction with a videotape of physical examination of the joints. So far, PI's have evaluated and taught over 700 individual examinations and have been involved in several continuing education workshops in the Tucson area.

The Tucson center also has developed a mini-residency program to provide an intensive educational program in rheumatology for primary-care physicians who have been in practice for a number of years. So far, 10 physicians and a nurse specializing in rheumatology have completed this program. Before their arrival at the center, candidates for the program complete an 18-page individual needs assessment questionnaire and send 10 arthritis-patient charts to be audited by the project director. Once there, participants complete a 5-day individualized tutorial with emphasis on their initially identified needs. A contract is written jointly by the staff and participant, listing changes and additions that will be incorporated into practice. Six months following the miniresidency, 10 arthritis-patient charts are again audited from the physician's practice, and a review and evaluation is made concerning contracted items.

The arthritis center at Stanford University in Palo Alto, California, for the past several years has been

developing a project to determine the effectiveness of community-based arthritis patient education, termed "arthritis self-management" (ASM). In a randomized, controlled trial, 300 persons taking the ASM course were found to have increased their knowledge and practice of exercise and relaxation techniques. In addition, pain was decreased, and trends toward less physical disability and fewer visits to physicians became evident. Arthritis self-management training has also been adopted by the National Arthritis Foundation for use by its local chapters. Arthritis center personnel have been active in providing training for Arthritis Foundation staff and volunteers to teach this course around the country. At present, over 3,000 individuals have participated nationally in ASM courses.

Patient education and group counseling are valuable in the management of patients with arthritis. The Multipurpose Arthritis Centers are assuming increasing responsibility for providing educational programs and materials for patients.

Center Community/Health-Services Research Projects

A study just being completed at the University of California's arthritis center in San Francisco is concerned with the long-term social and medical outcomes of total hip-joint replacement (THA). This operation is quite costly; approximately 90,000 operations are performed each year at a total cost of over $1 billion. Even though THA has been shown to be effective in relieving pain and restoring physical function in a large proportion of recipients, it has not, until now, been evaluated in terms of how it improves the quality of life and reduces disability. In the first year of the study, computerization of operating dates, diagnoses, record of prior surgery, prosthesis type, and basic operative data for 1,389 THA procedures were completed. After patients with complicating conditions, such as cancer, diabetes, or cardiovascular disease, and those who were too old to be expected to return to an active working life, were omitted, 178 persons agreed to participate in the study. All persons were questioned regarding their previous work history, job and occupational characteristics, and health status. It was found that work disability was significantly reduced after hip replacement surgery and that housewives also reported significantly reduced disability. It is noteworthy that patients who were operated on many years ago had the same probability of returning to work as those operated on more recently, in spite of technical improvements in the operative procedure. The next step of the study is to compare the actual costs of surgery with estimates of the benefits resulting from reduced disability.

The Center at the University of Tucson has been conducting a comprehensive analysis of the relationship of disability to building codes, with the goal of improving independent access to public buildings for all handicapped persons. Although many different accessibility codes have been developed for public and private building in the country, people with physical limitations often point out that many buildings still present access difficulties. The problem may exist because most modifications are based on the personal experiences of expert consultants or on testing with numbers of people that constitute statistically inferior representations of the total handicapped population. If more appropriate changes in building codes could be made, the costs of subsequent modifications could be reduced, and handicapped people would benefit from increased accessibility. As an example, most doorway sizes are based on the minimum width required for passage of a single wheelchair. In fact, the study discovered that although 90 percent of the subjects studied could be accommodated, 10 percent required up to 21 inches more space. Indeed, larger widths were required by some ambulatory subjects than by subjects using wheelchairs. It was also determined that siderails were usually placed too high to be reached by most handicapped people. Although the current standard is to have handrails placed 4 feet 6 inches high, 75 percent of wheelchair-bound subjects could not reach even 4 feet, and 25 percent of ambulatory persons could not reach 4 feet 5 inches. Recommendations incorporating these findings already have been included in building code deliberations at the national level.

The center at Boston University is studying the use of written health-status measures to detect small improvements in health status after treatment. In one study, center investigators compared the use of a written questionnaire with standard medical procedures in assessing the effectiveness of treating patients with rheumatoid arthritis with either gold or a placebo. Outcome was assessed both by standard procedures such as grip strength, laboratory tests, and physician and patient's assessments, and by the Arthritis Impact Measurement Scales. AIMS is a questionnaire that

estimates physical disability, psychological status, and pain. It was found in this drug trial that the AIMS questionnaire and physical findings produced essentially identical results. AIMS was thus quite sensitive to clinically meaningful drug-induced improvements. These findings support the use of this and other health-status indicators in clinical trials in rheumatology.

Core Units

During the past year, core units were in operation at several of the arthritis centers. These common-use facilities are designed to increase the effectiveness and efficiency of each center's activities. For biomedical research, there are core units for tissue culture, connective tissue metabolism, immunology, histocompatibility testing, and research involving hybridomas, to name just a few. Core units in other areas are concerned with biostatistics, evaluation methodologies, educational activities, and epidemiology.

The center located at Indiana University in Indianapolis has had two core units in operation during the past year. The first, dealing with immunology, has functioned as a centralized facility in which specialized tests of human immune function can be performed, including assays for immune complexes, assays of *in vitro* antibody synthesis, and assessment of T and B lymphocytes in peripheral blood. The other core, concerned with connective tissue biochemistry, has been designed to separate and purify proteins and other complex compounds derived from a variety of soft tissues. Thus, this core has developed the capability to separate substances by various types of electrophoresis and analyze the result by specially designed computer software.

A core unit at the University of Michigan's center is active in providing investigators with tissue-culture support for a number of diverse projects including: the isolation and characterization of proteins important in activating human connective tissue cells, a study showing that fibroblasts from scleroderma patients have increased rates of hyaluronic acid synthesis, and identification of a new connective tissue activator factor in human urine.

Collaborative Use of Resources Within Each Center

The shared facilities and cooperative effort made possible under the center concept permit more efficient use of resources and result in greater productivity than would be achieved by use of separate research grant awards to each of the participating individuals. Resource sharing is one of the major advantages of the center program, and it ensures maximal results from available funding. The centers provide an excellent example of the whole exceeding the sum of its parts.

Coordination and Collaboration Among Centers

A special emphasis of NIADDK program management is to foster and effect intercenter communication and activity, to make the MAC program more efficient and productive. One way of accomplishing this goal has been to sponsor annual meetings of center directors, center personnel, and Institute staff responsible for administering the program. Meetings of this nature, at which ongoing activities and plans are thoroughly discussed, provide an important opportunity for closer coordination among centers. In addition, the NIADDK centers program office annually compiles and updates a directory of center personnel, as well as a listing of instructional materials produced by the centers, and is in regular contact with each center by means of periodic letters and phone calls. The centers have also been encouraged to utilize the services of the Arthritis Information Clearinghouse, which is funded by contract by the NIADDK as a repository for educational and other information materials. This clearinghouse enables health professionals around the country to have access to literature produced by the centers during the course of their investigations.

As an example, the Stanford arthritis center is cooperating with the Boston University arthritis center to assess and cross-validate independently designed questionnaires used to determine how arthritis affects the quality of life. Ultimately, it is desirable to have a single set of outcome questionnaires to increase comparability of results. Both centers hope that collaboration will result in development of such questionnaires. Investigators at Stanford are also working with the staff of the Tucson center to modify Stanford's arthritis self-management course for use on the Papago Indian reservation and to prepare an arthritis self-management manual in Spanish.

Center Evaluation

In order to assure that the goals addressed by each center in its original grant application are being fully and successfully implemented, several types of evaluative activities are employed constantly. First, the centers evaluate continually both the quality and ef-

fectiveness of their endeavors. The evaluation mechanisms used vary according to the activity being studied, such as pre- and posttesting of students, chart audits of physicians who have received training, and process evaluation based on numbers of attendees at courses and lectures. Some of these measures, which may involve special evaluation core units, have already been described in this report. Many of the centers also have groups of outside consultants visit their institution for several days at a time each year to determine the quality of the ongoing activities.

In addition, the centers program office of the NIADDK monitors carefully the work of the various centers through staff site visits, analysis of yearly progress reports, letters and telephone calls, and the yearly meeting of the center directors.

On a more formal basis, a contract funded by the NIADDK to develop a methodology to evaluate the education and community components of the arthritis centers has just been completed. During the course of this contract, the contractor first gained a familiarity with the activities of the various centers and then, after close consultation with NIADDK program staff, formulated a number of specific evaluation questions to be addressed, together with an assessment of the best way to perform the evaluation, the resources required by both NIADDK and each center, and the optimal time for evaluation. In addition, the contractor has produced an evaluation guide to be distributed to each center to assure that each will maintain high evaluation standards.

Another measure of the effectiveness of a center can be gained by analyzing the results of the developmental and feasibility studies that it has supported. During the past 3 years, for example, the eight development and feasibility studies conducted by the center at the University of Alabama have resulted in 15 publications, 22 presentations at the national meetings, and 6 peer-reviewed and funded research grants.

Peer review plays a key role in evaluation of the Multipurpose Arthritis Centers in several ways: first, the NIH utilizes expert scientists as peer reviewers to conduct onsite visits and to review and evaluate each center grant application submitted; next, once in operation, most arthritis centers have an external advisory committee to oversee operations and provide advice on overall operations on an annual basis; and finally, before individual center projects are submitted for funding consideration, the arthritis center usually convenes a panel of internal reviewers to rate each project to assure that it meets the center's standards of quality.

Conclusion

The Department of Health and Human Services finds that the Multipurpose Arthritis Centers are continuing to progress significantly toward achieving their congressionally mandated objectives. This progress has been particularly evident during the past year, with notable maturation of the program involving high-quality research developments, prompt application of research findings in patient care, professional and lay education, broad collaboration with care providers, and productive demonstration activities. Progress made during the past year contributes to the fulfillment of the role of these centers as a national resource.

Sixth Annual Report on Evaluation of Diabetes Research and Training Centers

Introduction

The Diabetes Research and Training Centers program has been ongoing for 6 years. Authorization for the program was part of the National Diabetes Mellitus Research and Education Act (P.L. 93-354), which also made the establishment of this program contingent on recommendations of the National Commission on Diabetes (authorized by the same legislation). The current DRTC's are authorized under Section 435 of the Public Health Service Act and are listed in exhibit 6 (chapter I).

In its report to Congress (DHEW Publication No. (NIH) 76-1018), the Commission recommended that these centers promote the following types of activities.

(1) Basic and clinical research in the fields of diabetes and its management.

(2) Training of postdoctoral fellows for research in diabetes and its management.

(3) Training of health professionals in diabetes and its management.

(4) Training of practitioners of the health professions in diabetes and its management, in the form of continuing education and information programs.

(5) A model training-education-treatment demonstration facility for people with diabetes in order to contribute to the above four areas of endeavor.

At present there are seven such centers: Albert Einstein Medical College/Montefiore Hospital (Bronx), University of Chicago/Michael Reese Hospital (Chicago), University of Indiana School of Medicine (Indianapolis), University of Michigan (Ann Arbor), Vanderbilt University (Nashville), University of Virginia (Charlottesville), and Washington University (St. Louis). (Please see exhibit 6, chapter I.) Of the eight centers that were originally established, all have undergone at least one competitive renewal review, and seven have received continued funding. A renewal application from one center will undergo review during fiscal year 1984. Funding levels for these centers are shown in exhibit 13. The DRTC's are being evaluated continually through several varied but complementary processes, which include NIH peer review, review of progress reports, staff visits to centers, annual meetings, special evaluation projects by Institute staff, and in-house evaluations by centers themselves.

In keeping with the recommendations of the National Commission on Diabetes, the primary and most important prerequisite for institutions to establish a DRTC is an already existing substantial base of high-quality, independently supported research in diabetes and related endocrine and metabolic disorders. Within this environment, key participating investigators in each of the DRTC's undertake individually funded diabetes-related research and research training projects. The additional support from the center funding provides for shared resources (cores), pilot and feasibility studies for young investigators or investigators new to the field of diabetes, training and information transfer activities, and enrichment of the total research environment. An average of 62 percent of DRTC funding is devoted to biomedical research, including an average of 46 percent for biomedical core resources and 16 percent for pilot and feasibility research projects. For the training and information transfer component, which also embraces some clinical research support, an average of 38 percent of the funding is used; less than 1 percent of funding is used for enrichment activities.

Since the establishment of a DRTC is also dependent upon bringing together investigators from all relevant disciplines to work together in a multidisciplinary approach, the provisions of cores, as a feature that cuts across disciplines, is a very important aspect of a center. Pilot and feasibility research projects provide limited funding to young investigators or investigators new to the field of diabetes; these projects have been instrumental in attracting additional investigators to research in diabetes. The training and information transfer component, through the funding of cores, enhances clinical research and facilitates the transfer of new knowledge to a wide spectrum of health professionals responsible for the care and treatment of diabetic patients.

EXHIBIT 13. Funding levels of Diabetes Research and Training Centers in FY 1983 (dollars in thousands)

Albert Einstein College of Medicine, New York, N.Y.	$1,264
Indiana University, Indianapolis, Ind.	928
University of Chicago, Chicago, Ill.	1,827
University of Michigan, Ann Arbor, Mich.	1,917
University of Virginia, Charlottesville, Va.	1,044
Vanderbilt University, Nashville, Tenn.	1,121
Washington University, St. Louis, Mo.	1,567

This interdisciplinary approach has led to enhanced cooperative and collaborative efforts to address the problems associated with diabetes mellitus and has created a unique national resource. Outreach activities have provided prompt and effective transfer of new knowledge to health professionals. While each DRTC has developed its own independent program in accordance with local needs, interests, and resources, each is also responsive to national needs and works cooperatively with NIADDK and other federally supported

diabetes programs. The DRTC's also collaborate with relevant municipal, county, and state health agencies and coordinate their various activities with both local and regional medical associations and with appropriate voluntary agencies.

Thus, these centers have three principal distinguishing characteristics: (1) the prerequisite of an established base of high-quality investigator-initiated research in the area of diabetes and related endocrine and metabolic disorders; (2) funded shared resources (cores), which provide highly sophisticated techniques, methodologies, and equipment to foster interdisciplinary collaborations among investigators, more efficient and cost-effective procedures, enhanced quality control, an improved environment for clinical research, and other services that improve the quality of investigations fostering interdisciplinary endeavors; and (3) a training and information transfer component whose primary goals are fostering innovative approaches through new and improved methodologies, evaluating the resulting activities, and training all types of health professionals involved in the care, management, and treatment of patients with diabetes.

Types of Evaluation

Evaluation of the DRTC's is accomplished by four independent mechanisms: the NIH peer review system, organizations external to NIADDK, NIADDK staff, and individual center-based in-house evaluations. Evaluations at the centers concentrate on their own activities, materials produced by their training and information transfer component, and on preparation of progress reports and applications that intrinsically involve evaluation. Because all aspects of the local review process at centers are evaluated fully by the peer-review process, no further consideration of the evaluations conducted by the centers themselves will be included in this report. The other three approaches will be addressed here only briefly, since these evaluative processes have been described in detail in previous annual reports.

Evaluation by NIH Peer Review

The peer-review system of the National Institutes of Health provides a rigorous, thorough, and effective evaluation of the centers. This form of evaluation comprises an initial review group site visit to the proposed center and a subsequent independent review of the report of the review group by the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council. This two-tiered evaluation process serves as the primary basis for determining whether a center will be funded and for how many years (usually 3 or 5). At the end of this period, a renewal application may be submitted, the review of which includes a consideration of the progress made by the center toward achieving its goals and objectives during the previous period of support. Although conducted only every 3 to 5 years, the close scrutiny accorded this aspect of center evaluation makes it an extremely valuable, and indeed critical, part of the overall evaluative process. At the present time, all of the eight original centers have undergone competitive renewal review. One of these, although approved in principle, was judged not to have made sufficient progress toward accomplishing program objectives to merit continued funding.

Evaluation by Outside Organizations

National Diabetes Advisory Board

The National Diabetes Advisory Board (NDAB) has a mandate to oversee progress and make recommendations regarding the efforts by all relevant Federal agencies in implementing the *Long-Range Plan to Combat Diabetes* originally proposed by the National Commission on Diabetes (DHEW Publication No. (NIH) 76-1018). Within this comprehensive framework and after careful consideration of center activities, each report of the NDAB has addressed the progress of the DRTC program toward achieving its goals. In addition, the Board's advice and suggestions provide an ongoing external source of valuable guidance to the program. The NDAB's latest report (NIH Publication No. 83-2624, May 1983) stated, in part, regarding the diabetes centers:

> "Careful scrutiny and evaluation of these activities has again demonstrated the dedication and skills of the people involved. In spite of decreasing dollars and continuing demands to demonstrate growth and progress in a milieu of unstable support, these programs have served the diabetes effort extremely well through significant contributions to biomedical research advances, educational programs, new technology transfer, and effective collaboration."

Contract Evaluation

A final report has been received from a contract awarded to Performance Development Institute for a study to identify appropriate methods for evaluating the various center programs of the Institute, including the diabetes centers. Because NIADDK-supported centers are new and highly innovative programs that are still maturing and developing, the Institute was particularly interested in methods appropriate to formative evaluation, an evaluative approach designed to aid in the development of a program in its early phases. As a result of this study, it is apparent that evaluation at this time will have to be based on short-term outcomes. For the diabetes centers, most of these measures will not be particularly effective or reliable because complications of diabetes, the most appropriate outcome measure, take many years to develop. Thus, the effectiveness of such DRTC efforts as new treatments

or better or more intensive patient education cannot be ascertained over such a short timespan. Moreover, the complexity and the interdisciplinary and multidisciplinary aspects of these centers make such an evaluation prohibitively expensive at this particular time. Therefore, a decision has been made not to pursue this form of evaluation at the present.

Evaluation by NIADDK

Staff evaluations result from a variety of activities and resources, including applications, summary statements from reviews, progress reports, annual information requests on special topics, annual program visits to the centers, and various meetings of center participants. To cover outcomes of all activities of the DRTC's is beyond the scope of this report. In past reports, special topics relating to center activities and how these distinguish the center as a well-organized, goal-oriented, and effective amalgam of research investigators with special resources were presented. This report will follow the same basic approach and, in addition, will present some collective data relating to pilot and feasibility studies and to educational programs developed for health professionals, which are completed and are being put into more general use in settings outside the centers.

The Biomedical Research Component

The first two recommendations of the National Commission on Diabetes listed in the introduction to this report apply primarily to the biomedical research component of the centers. While investigator-initiated research and research training projects are the basis of this component, center funding provides many significant and important contributions. The major DRTC funding in this component is for biomedical cores or shared resources. How these cores facilitate the formation and organization of a center is addressed. The role of the pilot and feasibility studies as an integral part of the center effort also is discussed.

Biomedical Research Cores

A biomedical core at a DRTC is a shared facility that provides a service needed by, and available to, center research investigators and that will enable these investigators to conduct biomedical research more efficiently. The cores further serve as a focal point within the center for types of research in which the service provided is a necessary adjunct. There are also important functions and advantages, over and beyond the provision of the service, that are vital to bringing investigators together into an interactive multidisciplinary environment. These added benefits and catalysts for greater productivity are major distinguishing characteristics of the centers, and include: (1) greater collaboration; (2) availability of added consultation and training; (3) attraction of new and established investigators in other fields into diabetes research; (4) ready availability of large, expensive equipment and more efficient use of this and other equipment; (5) flexibility to pursue limited developmental research to ensure that the latest, best, and most needed services are available; (6) greater research productivity; (7) enhancement of clinical research; (8) generally, lower cost for service rendered through greater volume of service, bulk purchasing, sharing facilities with other large programs, quality control, and a center mechanism to screen requests, monitor usage, and prioritize needs; and (9) greater institutional support.

In order to illustrate these unique characteristics and show their relationship to the research efforts of a DRTC, some selected examples of recent research that involved using the cores and recent developments within or relating to the cores follow.

Collaborative efforts of research investigators at the University of Chicago DRTC involving the radioimmunoassay and clinical studies, peptide and protein analysis, and cellular and molecular biology cores have extended recent work on mutations in the structural gene for insulin. These mutations give rise to abnormal gene products (insulin variants), which are associated with diabetes. Continued studies in this area involve collaboration among many investigators in clinical research, gene cloning and sequencing, peptide chemistry, and human and animal physiology, both at the University of Chicago DRTC and elsewhere. Together these investigators have identified three individuals who secrete abnormal insulins and have studied the relationships between gene mutations and diabetes. These studies of the insulin gene in man have demonstrated the association of both clinical and basic research in investigating human disease. Although the incidence of insulin gene mutation is still not known with assurance, it may be considerably higher than previously thought. These investigations have provided new probes for studying insulin action and have emphasized the multiple areas of human genetics, hormone biosynthesis, hormone secretion, and hormone clearance in studying a disease as multifaceted as diabetes. These investigations were also the basis for presenting the 1983 Eli Lilly award to Dr. Howard Tager, DRTC director.

In addition, the 1983 Banting Award was made to Dr. Arthur Rubenstein, member and former director of the University of Chicago DRTC, for his work on proinsulin and C-peptide. Studies on proinsulin are continuing using human proinsulin prepared by recombinant DNA technology. This is the first time sufficient amounts have been available for clinical investigation of biological activity, metabolic characteristics, and therapeutic usefulness in insulin-dependent diabetic patients. These investigators have found that the clearance of human proinsulin is about four times slower than that of insulin; proinsulin also has a lower biological activity. Therefore, investigators are address-

ing the question of whether human proinsulin may be a valuable adjunct to insulin in the therapy of type I diabetes. Two new techniques that have been developed in the cores, a radioimmunoassay for proinsulin and the production of monoclonal antibodies specific for human proinsulin, will be extremely useful not only in these ongoing studies of proinsulin metabolism, but also in studying the hormone variants that may arise from insulin gene mutation.

Further evidence for the concept that such mutations as described by the University of Chicago DRTC investigators are more common than once thought comes from investigators at the University of Michigan DRTC. These researchers have been studying a subset of patients with maturity-onset-type diabetes in the young and those with noninsulin-dependent diabetes. In these patients, there are high or supernormal insulin responses to administered glucose as well as high basal levels of insulin. If insulin secreted by these patients had decreased biological activity, increased insulin secretion would be needed. A search for structurally abnormal insulin was conducted, and such mutants have been identified in several families through the use of core resources for immunoaffinity procedures and high-performance liquid chromatography to purify the insulin from these patients to a degree where its structure and function can be examined. Many other collaborators at the University of Michigan DRTC and other institutions also have performed studies that support these findings. If indeed these findings are common, they may contribute significantly to understanding the pathogenesis of one form of NIDDM. This area of research also demonstrates the integral functioning of a center that has brought together a variety of investigators with expertise in different areas to pool resources in a single, well-defined effort to unravel a hitherto obscure reason for abnormalities in insulin secretion in NIDDM.

One of the major areas of research at the University of Virginia DRTC addresses carbohydrate metabolism and regulation, which includes studies on glycogen metabolism, protein kinases and phosphatases, glucose transport, and insulin resistance in human tissues. Recent work has shown the existence of, and demonstrated some of the characteristics of, a family of small molecules located inside cells (mediators), which carry messages from insulin in the extracellular fluid into intracellular organelles. The mediators are located on the cell membrane. When insulin comes into contact with this membrane, the mediators are released and travel to parts of the cell carrying information related to the release of insulin. In all of these studies, the ready availability of the radioimmunoassay (RIA) core has played a very important part. Developmental work in the core, such as the development of an automated system to analyze more samples faster and cheaper also has had a major impact.

During the past year other significant developmental research has taken place in the University of Virginia DRTC RIA core. Investigators have completed development of an assay for glycosylated hemoglobin and for glycosylated albumin (which may represent a better monitor of diabetic control), increased the sensitivity of the assay for catecholamines, improved the synthesis of ^{125}I-cyclic AMP (which dramatically improved its specificity and stability), developed a new method for isolation of high-specific-activity mono-^{125}I-glucagon (which will vastly improve the glucagon assay sensitivity), and increased the sensitivity of the insulin assay tenfold by the use of more highly purified reagents. All of these developments represent new or improved techniques important to a wide variety of research investigators at this DRTC. Without the availability of the core as a focus for the development of these improvements, it is unlikely that such rapid progress could have been made or that the results could have been disseminated as quickly to investigators. It is clear that the core-center environment not only has improved research techniques but also has decreased duplication of effort.

Work continues by a group of investigators at the Washington University DRTC on transplantation of islet cells to cure experimentally induced diabetes in animals. Progress has been reported on three major obstacles to applying islet-cell transplantation in man: obtaining sufficient tissue for transplantation, selection of optimal anatomic sites for transplantation, and the need for long-term immunosuppression of HLA-dissimilar recipients. An improved method for isolation of islets involving the use of Velcro to remove the collagenous matrix of pancreatic tissue was described in this report last year. More recently, several anatomic regions have been identified as potential sites for islet transplantation: spleen, testicle, and peritoneal-omental pouch. The testicle seems to offer some degree of "immunologic privilege," but has an obvious disadvantage. The peritoneal-omental pouch is of practical significance because transplantation would be relatively simple and noninvasive, and the transplanted tissue could be readily isolated for subsequent examination or removal. Two approaches to the immunosuppression obstacle—understanding the mechanisms of islet rejection and developing a means of prolonging islet transplant survival without long-term immunosuppression of the transplant recipient—have been pursued. Both approaches are predicated on the theory that all cells have the antigenic determinants that may serve as the target for cellular immune rejection, but that some tissues lack the expression of the antigenic determinants (Ia antigens) needed for initiation of the process of immune rejection. Therefore, islets depleted of Ia antigen-expressing cells might be transplanted without the need for long-term immunosuppression of the host. Several encouraging techniques are being used to achieve this end. In addition, important advances have been made in developing alternate strategies to enhance immuno-

logic tolerance and islet graft survival. Core support for these studies comes mainly from the RIA core for measurement of hormones and the morphology core for light and electronmicroscopy studies. The latter core, because of its extensive use by a wide variety of investigators at the DRTC, underwent a major remodeling, modernization, and expansion by Washington University (non-DRTC funding) during the past year, which is an example of institutional commitment to a well-organized, extensively used resource supported by the center. Two individuals were recruited to the morphology core after it obtained initial pilot and feasibility funding—one is a new investigator, the other, an established investigator in basic immunology. One member of this group, Dr. Paul Lacy, was elected to the National Academy of Sciences last year.

At the Vanderbilt University DRTC, a major research effort relates to hormonal regulation, secretion, and interactions in carbohydrate metabolism. This work benefits significantly from the presence of a unique animal resources core. This core provides assistance, space, and equipment to center investigators who are conducting diabetes-related research on canine models of diabetes. The core provides animal care and monitoring, training of new investigators in experimental procedures, and development of new models for diabetes-related research in conscious dogs. The ability to prepare animal models consistently and reliably has significantly reduced variability and overall costs in this type of research. Techniques were established during the last year that permit measurement of hind-limb blood flow and that relate this flow to muscle mass, thus allowing assessment of the quantitative role muscle plays in the control of blood metabolites or hormone levels. These dog models were used in a recent study of the effect of epinephrine on glucose levels at constant insulin and glucagon levels. Not only was glucose production increased, but glycogenolysis and gluconeogenesis were stimulated. These studies will be extended to diabetic animals, where catecholamine (epinephrine and other similar compounds) levels are often higher than those studied initially, and gluconeogenesis is enhanced. Thus, these studies will extend our understanding of epinephrine's potential to antagonize the action of insulin in diabetes.

Another unique animal resource core, at the University of Indiana DRTC, maintains a breeding colony of Zucker rats, and because of the success of the breeding program, the DRTC has been able to offer them at cost to other investigators in this country. The Zucker rat is an animal model for obesity and for insulin resistance. During the past year, a diabetic variant of the fatty Zucker rat was characterized, and breeding stock are being developed. Recent research in insulin receptor regulation using the Zucker rat liver indicates that factors other than insulin concentration are involved.

The availability of human insulin prepared by DNA recombinant techniques has allowed a clinical study, at the University of Indiana DRTC, of the immunogenicity of a variety of insulins. An interesting observation from this ongoing study is that the amount of endogenous insulin, as measured by C-peptide, in patients never before treated with insulin, significantly altered their immunological response to injected insulin. Patients with more residual endogenous insulin secretion had less likelihood of developing antibodies to human insulin. The RIA core resource has been of extreme importance in this study.

At the Albert Einstein DRTC, a study on the impaired counterregulation of hypoglycemia in insulin-dependent diabetes mellitus demonstrated defective secretion of glucagon and epinephrine in diabetic subjects following insulin-induced hypoglycemia, which results in delayed hepatic glucose output. Thus, not only may diabetic patients be very susceptible to hypoglycemia, but the study suggests caution in attempts to keep IDDM patients' blood sugar levels in the normal range.

Greater efficiency and cost-effectiveness can be attained by several large programs sharing a single core resource, as evidenced by the mass spectrometry facility at the Washington University DRTC. This facility, provided by the Division of Research Resources, NIH, allows access to a technique that would probably not be available to center investigators alone. This DRTC has taken advantage of various unique aspects of stable isotope tracer use to expand human studies of metabolic fuel transport. Collaboration of the DRTC investigators with investigators from the Massachusetts Institute of Technology and from the Harvard Medical School has recently shown, by combined infusion of various carbon-13 and deuterium-labeled glucose molecules, that carbohydrate tolerance seen in elderly subjects was the result of impaired peripheral insulin effects and not the result of altered hepatic glucose homeostasis. Because the peripheral metabolism of glucose, particularly in muscle, is related to generation of muscle-released amino acids for gluconeogenesis and urea formation and because amino acid metabolism itself is also drastically affected by insulin actions in muscle, studies are now under way with infusions of (1-^{13}C)-leucine, (^{15}N) alanine, and (^{18}O)-urea to investigate the so-called branched-chain glucose-alanine cycle in elderly subjects. These studies should determine whether the operation of the cycle is quantitatively or qualitatively different in elderly subjects and in young adults.

In summary, these few examples typify the interactions that make the cores in the DRTC both integral and integrating factors in the interdisciplinary research approach. These examples also show other valuable byproducts gained from the establishment of shared resources. Thus, providing shared resources illustrates an advantageous and feasible approach to fostering

research efforts in an efficient and cost-effective manner for investigators from a variety of disciplines joined together in working on a disease as complex and multifaceted as diabetes.

Pilot and Feasibility Studies

Pilot and feasibility studies are another aspect of the biomedical research component of the DRTC's. Center awards provide modest support for a limited time period (3 years or less) for exploring the feasibility of a concept and amassing sufficient data to allow the investigator to apply for independent funding through the regular research grant mechanism. This mechanism provides a unique opportunity not only for testing new ideas, but also for young investigators to become involved in diabetes research and for established investigators in other disciplines to apply their expertise in the area of diabetes.

In 1980, a study of pilot and feasibility award recipients indicated that 40 percent of the recipients who had applied for NIH support succeeded in obtaining independent research support. Because the sample was small (61 individuals) and because the program had been in existence only 3 years, the study could not give any indication of whether these individuals would maintain their interest in diabetes research; therefore, a similar study was conducted again this year.

All pilot and feasibility studies that had been undertaken since the inception of the DRTC program (160 projects), except those that are currently active, were included. The recipients of these pilot and feasibility study funds were divided almost evenly between young or new investigators and established investigators new to the field of diabetes. Seventy-five percent of the studies were on basic biomedical research; 17 percent were on clinical research; and the remaining 8 percent were related to the training and information transfer component. The recipients also were divided almost evenly between those with M.D.'s and those with Ph.D.'s. One nurse and one dietitian were also recipients.

Overall, 44 percent of former recipients of pilot and feasibility funding currently hold NIH grants (R01, R23, and/or K series) on subjects closely related to those of the pilot and feasibility studies. Another 17 percent have similar funding from outside sources, such as the American Diabetes Association, Juvenile Diabetes Foundation, other foundations, and pharmaceutical companies. Nine other recipients have NIH grants pending.

Among young investigators who were awarded NIH grants, the same proportion held the M.D. as held the Ph.D. degree. Among established investigators from other fields currently holding grants in the areas of their pilot and feasibility studies, 38 percent hold an M.D. and 62 percent, a Ph.D. degree. Overall, of former pilot and feasibility recipients currently holding NIH awards, young investigators constitute the largest proportion (61 percent).

These results most certainly support the concept of pilot and feasibility studies within the centers, particularly as a mechanism for bringing new investigators into the field of diabetes research. However, it should be noted that these are still short-term data. Among the currently funded individuals, there were a significant number for whom this was their first grant in the diabetes area, and who will be coming up for renewal within the coming year. This analysis will be continued to examine the proportion of those who reapply and their degree of success in obtaining continued funding. Certainly, the results so far provide good evidence for the continued support of the pilot and feasibility studies at the DRTC's.

Training and Information Transfer Component

This component relates to recommendations (3) through (5) of the National Commission on Diabetes as presented in the introduction of this report. The last recommendation, relating to model demonstration units (MDU's), deserves some special mention in that it was to contribute to all of the other four areas of endeavor, including research. The MDU's were generally not proposed in initial applications, although all seven centers now have functioning units.They were designed mainly to facilitate activities (3) and (4). However, as the MDU's matured, their role in facilitating clinical research has become more prominent, and this role has served to bridge a gap that initially existed between the biomedical component and the training and information transfer component of the centers. For this reason, in this section, activities of the MDU's in relation to fostering clinical research will be described first, followed by some composite information relating to activities (3) and (4) and a brief overview of liaison activities of the DRTC's. The latter have been described in more detail in previous reports.

Model Demonstration Units

To best reflect the needs, goals, resources, and interests of individual centers, MDU's at the DRTC's were established in a variety of ways. All have some kind of limited patient-data system that is responsive to the activities of the individual MDU. As indicated, the design of the MDU's was intended for training health professionals and students in the health-profession fields to treat and care for diabetic patients. During the last 2 to 3 years, the availability of this resource for clinical research has attracted physicians and psychologists. The MDU, along with the other resources of the center, provides a number of unique advantages for clinical research: (1) an environment

separate from general clinics; (2) a patient-data system with reasonably well-characterized patient information; (3) an enhanced opportunity for collaboration with basic biomedical research scientists; (4) the possibility of initial funding as a pilot and feasibility project; and (5) services of the biomedical cores. Four relatively dissimilar projects that used an MDU were selected for brief presentation in this report to illustrate the potential that the presence of the MDU may have for fostering increased clinical research in diabetes and for providing a needed milieu for that research.

A study of autonomic dysfunction leading to paralysis of the stomach and small intestine in diabetic patients was funded as a pilot and feasibility study at the University of Michigan DRTC. In this study, a technique for measuring gastric emptying of both liquids and solids using a technetium-labeled resin was compared to the conventional pressure-motility patterns of paralysis, using balloons attached to strain gauges inserted into the gut. These investigators found excellent correlation between the two methods and have thus shown that a less-invasive procedure can be used to measure the extent of gut motility; this finding may have value in evaluating drug treatment to restore motility.

A physician and a psychologist at the Albert Einstein DRTC are collaborating on another study on performance, psychosocial, and physiological factors that contribute to improved metabolic control. The project follows 50 type I diabetic patients randomly assigned to either conventional or intensive treatment modalities utilizing the MDU, the patient-data system, the biomedical cores, and psychological measures developed at the center. Thus far, the study gives strong indication that psychosocial characteristics of insulin-dependent diabetics do not differ in any significant way from those of nondiabetic individuals. It is funded as a pilot and feasibility project.

Another pilot and feasibility study at the Washington University DRTC investigated the importance of family interactions for the level of control of diabetic youngsters. This research has shown that level of control is related to high levels of family cohesion and low levels of family conflict as reported by the child. Furthermore, level of control is greater among children whose parents report encouraging their children to behave independently and, presumably, to take greater responsibility for their disease management. This research has been the subject of several publications.

At the University of Chicago DRTC, a study on the use of an aldose-reductase inhibitor in the treatment of diabetic neuropathy was supported mainly by non-NIH funding, but used the MDU facility. Twenty-one diabetic patients were studied in a randomized, double-blind, crossover format to assess the efficacy of Sorbinil in altering the course of diabetic neuropathy. This aldose-reductase inhibitor was considered as a potential agent for reversing this complication of diabetes. Investigation of the drug's action over a period of several months showed that motor nerve conduction velocities improved in diabetic patients receiving Sorbinil. The improvement was statistically significant and indicates the potential for use of the drug. Since neuropathy is an important and common complication of diabetes, the beneficial effect of the drug on motor-nerve function in diabetic patients gives reason for optimism that it may be useful for prevention and/or treatment of diabetic neuropathy.

Psychosocial or behavioral investigation of diabetic patients was identified by the National Commission on Diabetes as a needed research area that centers were encouraged to consider. Ready access to a characterized patient population and a suitable environment for such studies are provided by the MDU. Clinical research in diabetes also has been identified as an area for additional attention. Use of an MDU, access to services from biomedical cores, and the availability of potential collaboration with basic biomedical scientists, provide an encouraging environment. The potentials for increased clinical research, with concomitant encouragement for physicians to engage in careers in research, should be pursued and nurtured within the centers.

Programs and Materials for Health Professionals

In previous reports, selected programs or materials developed were described in some detail. For this report, some composite data relating to the type, number, and status of the most well-developed of these activities are presented in tables I and II. These data will serve to illustrate the breadth and scope of programs and materials now available from the DRTC's. The following narrative provides some further explanation and amplification of the data and some other activities that do not fall into these categories.

Data on Programs and Materials Developed

For the compilation in table I, only written materials that are being disseminated at present, or that will be ready for dissemination in the near future, are included, and these are assigned to one of five categories. The "Curricula" are teaching manuals for use in training courses for health professionals. Of the 17 curriculum items (column 1), 3 are directed toward physicians, 2 to nurses, 3 to dietitians and nutritionists, and 9 to (all) health care professionals including teams. They are considered to have been evaluated (column 2) if pre- and posttests (or the equivalent) plus one other evaluative measure have been employed, and further evaluation has been completed or is ongoing.

Depositing material with the National Diabetes Information Clearinghouse (column 3) ensures that knowledge of the availability of the material will be more widespread. A compendium of these and other similar resources is currently being compiled by the NDIC. In addition, the centers themselves utilize a variety of mechanisms to bring these materials to the attention of appropriate audiences. Over half are presently being used outside the centers (column 4), either regionally or nationally; many others are still being evaluated.

The second category in table I lists evaluation methodologies, which are instruments needed for evaluation of the other materials and include assessments, surveys, knowledge acquisition tests, simulations, and compliance measurement. It is not surprising that fewer evaluation methodologies are deposited with the NDIC or in use outside the center because they were generated primarily for evaluation of programs being developed.

Three centers have prepared documents relating to standards of care (row 3). These standards are important adjuncts to training of health professionals. The fourth category relates to materials for patient education that were developed for use by health professionals. Some of these are used in conjunction with the curricula. The subject matter is varied and includes manuals for improving patient education programs, for self-management, for weight loss, and for exercise; knowledge tests for patients in diabetes camps; and pamphlets on various aspects of diabetes for patients. Some of these materials also are included with the curricula, and hence not many have been deposited separately with the NDIC.

The last category, resources, contains only three items: (1) an audiovisual catalog of available diabetes-related materials and a user's guide, which has been published and has had wide dissemination; (2) a community resources directory, which is a part of an outreach program and thus far has had only local use; and (3) an annotated listing of journals, which may be sources for publication of behavioral medicine research relating to diabetes. Since behavioral medicine research is a developing area relative to diabetes, channels for publication are not well established. As a result of discussing the reasons for this situation with journal editors, one issue of *Occupational Health Nursing* was recently devoted entirely to diabetes-related topics.

Continuing medical education (CME) courses that are currently being offered by the centers are analyzed in table II. In many cases, the materials developed (see table I) are used in conducting these courses. Over two-thirds of the courses are from 2 to 5 days in duration.

Table II shows the number of such courses by health profession and by subject area. "Fundamentals" refers to a wide coverage of many aspects of diabetes and may include aspects of the other six subject areas listed. Courses on new advances are almost exclusively on the use of home blood-glucose monitoring and use of continuous subcutaneous insulin infusion (pumps). Because nutrition is such an important part of good diabetes care, it is not surprising that a significant proportion of the courses address this subject. "Methodology" refers to courses designed to teach evaluation methods, assessment making, strategy planning, strategy implementation, and educational techniques. The significance of such activities lies in the facts that evaluation of educational programs and investigation of alternative teaching strategies are possible only with the use of reliable and valid measures to assess knowledge and adherence. This type of instruction is particularly important if, as is expected, health professionals taking these courses in centers in turn pass on their knowledge to others in their local settings. Psychosocial issues were identified by the National Commission on Diabetes as an area of needed attention. Through pilot and feasibility studies, mentioned before, these CME courses also contribute to filling the gap prior to project funding. "Complications" refers to courses addressed specifically to one complication; however, complications may also be addressed in the courses on fundamentals. Recently much more attention has been placed on the balance of exercise, insulin, and food intake. This new emphasis is another example of the centers' fulfilling a newly emerging need.

DRTC Liaison

Interaction of the DRTC's with other major diabetes groups, and their utilization as a national resource by them, has been encouraged from the inception of the centers. Most of these endeavors are ongoing, and some have been described in detail in earlier reports. In this report, these activities will be summarized for all centers, rather than as specific examples.

An important facet of this interaction is a close working relationship with the voluntary health agencies related to diabetes—most notably the American Diabetes Association and the Juvenile Diabetes Foundation. This relationship was established and used very early and covers a wide spectrum of activities. In many cases, CME courses are cosponsored by the center and the voluntary agency. Both the University of Chicago and Washington University DRTC's have hosted the JDF annual conference for medical students, designed to stimulate an early interest in diabetes and diabetes research. The cooperation of these groups with all centers has been exemplary.

The Centers for Disease Control (CDC) Diabetes Demonstration Projects were established at approximately the same time as the DRTC's. Through funding to state health departments, this program supports discrete demonstration projects in an effort to effect changes in state and local health systems and to reduce morbidity and mortality from diabetes. The DRTC's

collaborate primarily by presenting CME programs, collaborating in interventions, serving as consultants to the CDC program review, and supporting pilot and feasibility projects that include collaboration with a state program. There are mutual benefits to both diabetes programs from these collaborations. The close working relationship that exists precludes duplicative endeavors. Cross-fertilization is aided significantly by attendance at annual meetings of each program by participants from both groups.

The DRTC's are also collaborating with the Model Care Diabetes Program of the Indian Health Service (IHS), a component of the Health Resources and Services Administration. Diabetes mellitus is a serious and widespread problem in the American Indian population; in some groups, the prevalence of diabetes is as high as 50 to 60 percent. The IHS is examining the effect of providing education and training in diabetes to IHS personnel, in a feasibility study being conducted at five selected locations. Personnel from the DRTC's act as consultants and present their education and training programs. They also are furnishing selected materials, which they have developed, to be incorporated into special programs that will be most appropriate for a particular tribal group. This experience is valuable to the centers in evaluating the effectiveness of some of their training programs in a separate population and culture of defined population characteristics; the collaboration will also benefit the IHS program by making available training programs and needed medical expertise in diabetes during the development of a viable program.

There is also considerable involvement of DRTC's and their staffs in the Diabetes Control and Complications Trial, funded by the NIADDK, to determine whether normalizing blood glucose helps to prevent or ameliorate diabetes complications. Two diabetes center institutions are participating clinical centers in the trial. Two principal investigators of DRTC's serve as chairpersons on committees for the trial, and other DRTC participants are members of committees. Many DRTC members served as *ad hoc* consultants during the design phase, particularly on the educational and psychosocial aspects.

The National Diabetes Advisory Board is a legislatively mandated body to oversee progress and make

TABLE I. Tangible materials developed

Category	Number Developed	Number Evaluated	Number Deposited with NDIC*	Number Currently in Use Outside Center
Curricula	17	15	10	9
Evaluation methodologies	11	10	3	2
Standard of care	3	3	1	3
Patient materials	9	9	2	2
Resource compilations	3	2	3	3

* *NDIC = National Diabetes Information Clearinghouse*

TABLE II. Continuing medical education programs for health care professionals

Subject Area	Number of Programs	Type of health professionals addressed: Physicians	Nurses	Dieticians or Nutritionists	All Health Professionals	Health Professional Teams
Fundamentals	28	7	8	7	4	2
New advances	16	5	5	3	3	
Nutrition	14	1	1	11	1	
Methodology	8		3	2	3	
Psychosocial	7		1	1	3	2
Complications	3	2	1			
Exercise	2		1		1	

recommendations regarding Federal efforts in diabetes. The NDAB also provides the umbrella for the development or stimulation of needed activities in relation to diabetes. An NDAB conference in 1980 identified a need for the preparation and publication of *The Prevention and Treatment of Five Complications of Diabetes: A Guide for Primary Care Practitioners*. This booklet was prepared with a major commitment of time and expertise from one of the DRTC's and CDC. It was pretested and printed for distribution early in 1983. To test feasibility, it was introduced first in the Federal sector in February 1983 at a conference sponsored by the Diabetes Mellitus Interagency Coordinating Committee, in which CDC played an important organizational role. The University of Michigan DRTC, under contract with the CDC, prepared slide sets and a written narrative to accompany the *Guide;* these are presently available. In a second printing of the *Guide,* the DRTC's ordered copies for use in conjunction with their programs. The DRTC's will further explore its utility, since DRTC staff will be available as consultants. Two centers have already planned to design evaluation instruments. The *Guide's* dissemination will be monitored by an advisory group that will include representation from the DRTC's.

Interaction and collaboration by the DRTC's with both Federal and private groups with substantial interests or programs in diabetes was recommended by the National Commission on Diabetes. It has subsequently been encouraged by the NDAB. Some new activities are initiated each year and, in general, ongoing activities have been continued or expanded.

Conclusions

The Department of Health and Human Services finds that the diabetes research and training centers are continuing to progress significantly toward achieving their congressionally mandated objectives. Of particular interest are the many advantages that accrue from shared resources (cores) over and above the services to research investigators from the cores. Clinical research is improving at each of the centers, in part due to the presence of a model demonstration unit core for the center. Many training programs for health professionals have been developed and evaluated and are being utilized in many settings outside the center. Liaison with other significant diabetes programs continues to expand. Progress made during the past year contributes to the fulfillment of the role of these centers as a national resource.

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